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The next issue will treat of: MULTIPLE SCLEROSIS

Editorial

El síndrome Parkinsoniano constituye uno de los cuadros clínicos más evidentes de la medicina debido a sus característicos signos exteriores.

El diagnóstico puede ser hecho con solo mirar al enfermo, a veces cruzándose con él en la calle.

El rostro del parkinsoniano es conocido de inmediato por su inexpresividad, su fijeza de máscara.

La rigidez del dorso inclinado hacia adelante, la marcha dificultosa a pasos cortos, de quien se siente adherido a la tierra, el temblor de las manos en movimiento casi perpetuo, la voz monótona y apagada, con la que repite una y otra vez la misma frase; la dificultad en la ejecución de los movimientos automáticos asociados (faltan las oscilaciones de los brazos en la marcha), son elementos inconfundibles en esta clase de pacientes.

Pero lo evidente y claro en el síndrome Parkinsoniano termina con su cuadro clínico, puesto que otros aspectos de este síndrome son todavía oscuros y hay numerosos problemas aún sin solución.

James Parkinson, un médico práctico de Londres (1755-1824), fue el primero en describir esta enfermedad, la cual, desde entonces lleva su nombre.

En su "Essays on Shaking Palsy" (1817) escribió acerca de este malestar en la siguiente forma: "temblor en el reposo, aún sosteniendo la parte afectada, con disminución de la fuerza muscular, tendencia a inclinar el tronco hacia adelante y a aumentar sin causa mientras camina, la rapidez de su paso; los sentidos y el intelecto están intactos".

Por mucho tiempo esta enfermedad ha sido confundida con la Esclerosis en Placas, hasta que fue diferenciada claramente por Cohn (1860), Ordenstein (1867) y Charcot (1872). Marshall Hall le dio en 1841 el nombre de Parálisis Agitante.

Hace alrededor de 40 años, en ocasión de una epidemia extendida por todo el mundo, de grippe y encefalitis, aparecieron en distintos países casos de síndrome Parkinsoniano en gente joven.

La encefalitis infundía al cuadro parkinsoniano algunas características especiales y en los tratados de neurología aparecidos posteriormente comenzaron a describirse diferencias entre el Parkinson post encefalítico y el Parkinson esencial. Pero todo esto tiene actualmente un valor relativo dado que en estos momentos con ser tan frecuente el síndrome Parkinsoniano apenas se comprueba la etiología post encefalítica.

La gran mayoría de los casos aparecen sin una causa conocida entre la 5ª y 6ª década de la vida.

A veces su origen es atribuído a la arterioesclerosis; pero en los cuadros clínicos típicos esta relación etiológica no es clara por falta de prueba anatómica indiscutible.

Muy rara vez los síntomas parkinsonianos han aparecido después de intoxicaciones con monóxido de carbono.

La forma más frecuente es la llamada enfermedad de Parkinson o Parkinson esencial, cuyo origen es totalmente desconocido. Dentro de las posibilidades que ofrece actualmente un planteo etiológico, habría que pensar en una perturbación metabólica del tejido nervioso o en factores extrínsecos aún no precisables. Tampoco se sabe en qué consiste lo íntimo del trastorno neuronal y qué es lo que lo pone en marcha.

La anatomía patológica muestra lesiones extensas y con cierta variación según los casos, siendo difícil saber cuáles son las que justifican la aparición de los síntomas. las localizaciones más constantes son en el globus pallidum y en la sustancia nigra.

La topografía de las alteraciones anatómicas debe necesariamente hacer pensar en mecanismos fisiopatológicos. Estos sin embargo siguen siendo una incógnita.

El Parkinsonismo está en el grupo de los síndromes extrapiramidales, es decir, es un cuadro clínico en el que predomina un disturbio motor de origen central, que no es producido por una deficiencia en las fuerzas (paresia o parálisis) al modo de lo aue ocurre en un hemipléjico (síndrome piramidal), en el cual, en cambio, hay perturbaciones en la regulación del tono muscular, en las actitudes posturales, en la ejecución de los movimientos automáticos asociados, y pueden existir movimientos anormales.

Se piensa que esto es debido a lesiones en el llamado Sistema Extrapiramidal. En la experimentación animal (monos, etc.), no ha sido posible obtener por lesiones del globus pallidum y de la sustancia nigra, el síndrome Parkinsoniano.

La cirugía estereotáxica (cuando actúa sobre el globus pallidum) puede mejorar en forma dramática algunos de los síntomas parkinsonianos, lo cual nos coloca en la difícil posición de admitir que los síntomas debidos a una enfermedad del pallidum, mejoran cuando se realiza en éste una lesión más profunda.

Para que exista temblor es preciso que la vía piramidal esté intacta.

Los impulsos nerviosos que son conducidos por ella son necesarios para producir los movimientos rítmicos.

La lesión piramidal espontánea (hemiplejía, debida por ejemplo a un reblandecimiento o hemorragia) o provocada quirúrgicamente (operación de Putnam), detiene el temblor.

Algunos autores sostienen que la cirugía estereotáxica que también interviene sobre el tálamo, es exitosa sólo en la medida en que la vía piramidal está afectada.

La aparición de cuadros de Parkinsonismo por acción medicamentosa (compuestos ataráxicos), ha hecho pensar que existen elementos constitucionales en su determinismo y quizá esto permita estudiar la importancia relativa de los factores genético y exógeno en la génesis de sus distintas formas.

Ultimamente estos problemas fisiopatológicos se han visto iluminados con los nuevos adelantos de la Neurofisiología, así la Formación Reticular por un lado y las fibras motoras gamma por otro, han sido tomadas en consideración en la interpretación de este complejo problema clínico.

Estamos convencidos que este número, dedicado al Parkinsonismo, con las valiosas contribuciones de los Dres. Leonard T. Kurland y Richard W. Darrell (Bethesda); Dr. D. Denny Brown (Boston); Dr. Geofrey Rushworth (Oxford); Dres. Thomas R. S. Scott y Martin Netsky (North Carolina); Dr. Robert S. Schwab (Boston); Dres. V. Talairach, P. Tournoux, G. Szikla, A. Bonis y V. Bancaud (París); debe ser considerado como una puesta al día de esta enfermedad de excepcional jerarquía.

VICTOR SORIANO.

Editorial

The Parkinson Syndrome constitutes one of the most evident pictures found in Medicine due to its recognizable external signs.

The diagnosis can be had by only a glance at the patient even passing by him in the street.

Among the many faces with their varied expressions that pass in a day, the Parkinson one is spotted inmediately because it has no expresion, only a frozen mask. Behind the intelligence may glow in the eyes peering through the portholes of a wooden façade.

The rigid backbone, the back and shoulder bowed, and little steps are taken with the difficulty of one who feels himself stuck to the earth. But look at his hands. They are in perpetual motion, the only livable sign of energy which leaks through the extremities of the forelimbs. If you happened to address him, a voice monotonous and flat, rumiates again and again the same sentence unable to express the feelings and thought of an intact intellect. A muscle-locked man, the patient has difficulties to perform associated movements. From rising in the morning he begins a difficult journey through the day.

But the clear evidence of the Parkinson's syndrome ends with its clinical picture, since several other aspects of this illness are still obscure and there are numerous problems still unsolved.

James Parkinson a London practitioner (1755-1824), was the first to describe this illness which ever since has bourne his name.

In his "Essays on Shaking Palsy" (1817) he wrote about this ailment as consisting of "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and intellect being uninjured".

For a long time this illness has been confused with Multiple Sclerosis, until it was clearly differentiated by Cohn (1860), Ordenstein (1867) and Charcot (1872).

Marshall Hall gave it the name of Paralysis Agitants in 1841.

Nearly forty years ago, on the occasion of a world wide epidemic of grippe and encephalitis, a Parkinson syndrome in young people appeared in several countries.

Encephalitis gave to the clinical pictures of Parkinsonism certain special characteristics and in neurological treatises the differences between Parkinsonism post encephalitic and the essential Parkinsonism are established. But all this has a relative value at present, since in these days the Parkinson cases are very numerous, this etiology is not frequently encountered. Most of the cases appear without any recognizable cause in the fifties or sixties.

For sometime it was believed that arteriosclerosis was a cause, but in the clinical picture the etiological relation is not clear enough due to a lack of clear anatomical evidence.

The Parkinson syndrome very seldom has appeared after a carbon monoxide intoxication.

The most frequent form is the desease called Parkinson or essential Parkinson whose cause is completely unknown. Among the possible etiological esplanations now being offered, a metabolical disturbance of the nervous tissue or extrinsic factors not yet detected would be necessarily considered. Also unknown are the interior process of the neuronal trouble and what sets it off.

The pathology reveals widespread lesions with certain variations in each case. It is difficult to tell which are those capable of bringing on the symptoms. The localizations most consistent are in the globus pallidus and in the substancia nigra.

The topography of the anatomical alterations should necessarily lead us to think about its physiopathological mechanisms.

Nevertheless they continue to be unknown. Parkinsonism belongs to the group of the extrapyramidal syndromes, that is a clinical picture in which disturbance of central motor origin exists, which it is not produced by a deficit in strength (paresis or paralysis) as occurs in hemiplegic patient (pyramidal syndrome).

In Parkinsonism there are instead impairment in the regulation of muscular tonus, in the performance of automatic movements, in posture, in the execution of associated automatic movements and besides may exist involuntary abnormal movements.

It is thought that this is due to lesions in the so called extrapyramidal system.

It has been remarked that the lesion of the globus pallidus and the substancia nigra could be the most important reason for the appearance of the symptoms, despite the fact that until now nobody has been able to reproduce in laboratory animals (monkey, etc.) a Parkinson's syndrome with the lesion of these structures.

Stereotaxic surgery (operating on the globus pallidus) may improve some of the Parkinsonian symptoms in a dramatic way, which places us in the contradictory position of admiting that the symptoms due to a lesion of the pallidus, improve when a deeper damage is inflicted upon it.

The pyramidal tract should be intact for there to be a tremor.

The nervous impulses that travel through it are neccesary to produce the rythmical movements.

The spontaneous pyramidal lesion (hemiplegia due to for example a vascular lesion) or inflicted by surgery stop the tremor.

Some authors believe that the stereotaxic surgery that also acts upon the thalamus, is only successful to the exent that the pyramidal pathway is damaged. Lately these physiopathological problems have had new light thrown upon them with the new advances in Neurophysiology, and so the Reticular Formation *on one side, and the* gamma motor fibers *on the other, has been taken into consideration in the unraveling of this puzzling clinical problem.*

With the therapeutic use of ataraxic compounds sometimes a picture of Parkinsonism can be observed. Studies of the possible constitutional factors in this reaction were suggested as step in defining the relative roles of genetics and exogenous factors in this Syndrome.

We are convinced that this issue dedicated to Parkinsonism due to the very valuable contributions given by Drs. Leonard T. Kurland and Richard W. Darrell (Bethesda); Dr. D. Denny Brown (Boston); Dr. Geofry Rushworth (Oxford); Drs. Thomas R. S. Scott and Martin Netsky (North Carolina); Dr. Robert S. Schwab (Boston); Drs. V. Talairach, P. Tournoux, G. Szikla, A. Bonis and V. Bancaud (Paris) must be considered as an up to date broad resumé of this illness of exceptional hierarchy.

VICTOR SORIANO.

Epidemiologic and Genetic Characteristics of Parkinsonism: a Review

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Introduction

The measurement of the geographic distribution of a disease may at first glance appear to be a simple matter, to be answered from personal clinical experiences or hospital record analyses. But the many papers comparing case series and hospital admission rates provide only a general impression of the frequency of illnesses, and cannot be used for accurate statistical comparisons. Reliable incidence data in different geographic areas are assential for the description of the natural history of a syndrome, may provide clues to causative factors, and aid in the planning for future needs of medical facilities and personnel. However, suitable population statistics are scarce indeed, and those which are available can be compared only after the local variables affecting diagnostic practices and the recording of cases are recognized and evaluated.

The purpose of this report is to discuss the frequency of Parkinsonism based on selected mortality and morbidity surveys, and to comment on the role of genetic and epidemiological factors in the disease. Two current studies will be referred to: one, a genealogical analysis of relatives of patients who developed Parkinsonian symptoms while on treatment with ataraxic drugs; and the other, a study of a geographical isolate of a condition referred to as Parkinsonism-dementia complex on the island of Guam.

If we can agree upon a clear definition of a "case" so that the affected can be distinguished from the unaffected in a population, statistical comparisons can be made, preferably through incidence or prevalence rates. An incidence rate is the number of newly developed (or newly discovered) cases of an illness, during a specific time, in relation to the population "at risk" of developing the illness. Incidence rates are usually expressed as the number of cases per hundred thousand population per year. They most effectively characterize illnesses of clearcut onset, acute course and short duration. Mortality rates are a type of incidence measurement limited to those who die of a specific cause. Prevalence is the number of cases that exist in a population at a given moment, or more realistically, on a certain date. Prevalence rates are especially useful in describing a disease such as Parkinsonism, of insidious onset and long duration.

Between the recognition by the family or the patient that the latter's health has changed, and the recording of the diagnosis in the hospital index or the National Office of Vital Statistics mortality code, there are four levels at which errors affecting measurement of disease frequency may be made. First of all, the subject must be recognized as being ill. A Parkinsonian tremor may often be accepted as a "normal" feature of the elderly. Secondly, the patient, in addition to recognizing his illnes, must seek medical attention. In the Guam disease, individuals with obvious symptoms of Parkinsonism associated with dementia are often completely unaware of their illness and would not have been diagnosed if relatives had not brought them in for medi-

cal attention. Thirdly, the physician must make an appropriate diagnosis. The variations in diagnostic practices in different nations may make hazardous the comparison of incidence or prevalence rates. The best we can do in an exploratory survey is to accept the local designation of a case, with a clear description of the local diagnostic criteria. Fortunately, Parkinsonism has no special social stigma, so that relatives and psysicians are not reluctant to report cases. Finally, the physician's diagnosis must be correctly reported in a survey, coded and filed at the local hospital or, if the patient dies, reported on the death certificate and coded by the Office of Vital Statistics. There is no compulsory reporting of current cases of Parkinsonism other than those affiliated with various national health or other insurance programs.

Mortality Statistics

Comparative mortality rates give general impressions of the frequency and geographic distribution of Parkinsonism for large areas and populations. It is important to recognize the limitations of death records and of the mortality statistics compiled from them. To compare statistics from two areas we must ask: how similar is the quality of medical practice, how reliable are the diagnoses, how complete is the certification to central offices, and how uniform are the coding practices? National mores and customs may influence autopsy practices and other factors which contribute to variations in the accuracy of cause of death reporting. In some countries, physicians preparing death certificates may list only one cause of death. If a patient has a serious underlying chronic illness as well as an acute disease which is the immediate cause of death, only the acute disease may be recorded, and the underlying cause omitted. This point is illustrated in the study of Canadian death certificates for 1951 in which Parkinsonism or paralysis agitans were reported as either the underlying, or a contributory cause of death(1). Of the 529 such certificates, Parkinsonism was reported as the underlying (primary) cause of death in only 46% of the cases, and as a contributory cause in the other 54%. The crude death rate per 100.000 population based on the 46% is 1.7, whereas it becomes 3.7 when the other group is added. Thus, the mortality rate for Parkinsonism based on the reports listing underlying cause of death alone, will be an erroneous underestimation of the actual death rate.

Age at Death: The most complete age specific mortality rates available for Parkinsonism are based on the 1951 Canadian statistics, which show that the rate is nil below age 50 years but then increases rapidly with age. The median age at death is 72 years(1).

Death Rates by Sex: In every age group, the death rate based on the 1951 Canadian certificates is slightly higher for males than for females(1). For all ages combined, the rate per 100.000 population is 2.1 for males and 1.7 for females (1.2 to 1 ratio) using records listing underlying causes only, and 4.3 for males and 3.0 for females (1.4 to 1 ratio) when both underlying and contributory causes are combined.

In the United States the death rate is slightly higher for males than females: for the years 1953 through 1955, the rate per 100.000 population based on underlying causes of death only, was 1.9 for males and 1.5 for females (a ratio of 1.3:1)(1, 2).

The degree to which the mortality statistics underestimate the actual frequency of a disease is illustrated by a survey in Rochester, Minnesota(1). It was found that of all persons known from clinical reports to have Parkinsonism at the time of their death, Parkinsonism was mentioned on only 20% of the death certificates.

Geographic Aspects, Canada and United States: An effort was made to determine whether there was a significant pattern of geographic distribution, but the age ajusted rates for Canada and for the white population in various regions of the United States fall within the comparative narrow range of 1.3 to 1.9 per 100.000 population per year(1, 2). The small regional differences are probably caused by variations in the relative completeness of cause of death reporting rather than by any significant geographic selectivity.

Comparison of rates by race: The rate

for the white population of the United States is greater than that for the non-white population, but this again may be related to differences in medical care and mortality reporting(2).

Trends: There is no apparent annual change in the death rates in the United States for the years 1949 to 1955(2).

International Mortality Rates: A study recently completed compares mortality statistics of a number of neurological diseases in 25 countries throughout the world(3). The age adjusted rates per 100.000 population show a rather wide range — from 3.8 in Australia to 0.5 in the non-white population of the United States and the populations of Mexico, Japan and Czechoslovakia. In view of the many factors affecting these statistics, it is uncertain how much of the difference represents diagnostic or reporting artifact, and how much represents geographic trends or population selectivity for the disease.

Morbidity Surveys

Reports comparing the relative frequency of a disease using hospital admission rates are subject to several sources of bias that affect differential incidence. However, one hospital study which has some merit, is an analysis of 7.941 individuals over 61 years of age, admitted to the medical service of the Peter Bent Brigham Hospital in Boston for 30 years prior to March, 1943(4). Of these, 81 or 1% showed paralysis agitans without psychosis, while an additional 40 patients, or 0.5%, had cerebral arteriosclerosis, psychosis, and paralysis agitans. Mettler(5) of Columbia University, surveyed several homes for the aged in New Jersey and New York, and reported that for inmates 65 years and over, the prevalence rate of Parkinsonism was about 24 per 1.000. All inmates were examined individually to insure a complete morbidity count. The difficulty with these studies in that neither patient group is representative of the general populations from which they are derived, since they include a higher proportion of elderly people who are disabled and have locomotion defects and self-care problems.

In 1949, Mjones(6) surveyed selected clinics for cases of Parkinsonism and reported that, for persons aged 50 years and older in Sweden, the minimal prevalente rate was 1.6 per 1.000. Garland(7) surveyed a group of practitioners serving a population of 485.903 in and around Leeds, England. He was notified of 288 cases of Parkinson's disease and calculated a prevalence of 0.6 per 1.000 for all age groups. Both surveys are probably incomplete and provide only a minimal estimate of prevalence.

A survey of various illnesses, including Parkinson's disease, was carried out in 1950 by the Canadian Government under the title "Canadian Sickness Survey"(8). This consisted of personal interviews without physical examination, carried out by trained enumerators who visited approximately 10.000 randomly selected households comprising 33.000 persons in Canada distributed throughout each of the ten provinces. The prevalence rate per 1.000 population for Parkinson's disease was approximately 0.3 for all ages; 0.85 for age group 45 to 64 years, and 1.5 for age group 65 year and over(9).

In contrast to the sample survey techniques of the Canadian study, a study in Rochester, Minnesota was based on an analysis of records of all clinically identifiable cases occurring in the local population during the period 1945-54, inclusive(1). In most cities it would be impossible to enumerate all cases through medical records alone because most hospitals do not cross index patient visits to clinics and private physicians and, furthermore, in most cities the majority of physicians primarily practice outside the hospitals. In Rochester, however, the large majority of local residents with progressive serious illnesses seek medical aid at one of the Mayo Clinic facilities. The Clinic diagnostic records are coded in a unified record system whether the patient is hospitalized, seen at the outpatient clinic, or by the Clinic physicians in the hospital or at home. During the period of the study there were only a few physicians in general practice in the community, and case reports were sought from them concerning additional patients who were or had been under their care. Further case reports were derived from the nearby State Mental Hospital, County

Community Hospital, and from the local Office of Vital Statistics. The definition of a case for the purpose of this study was one in which the clinical diagnosis of paralysis agitans or Parkinson's disease was so recorded and no later clinical report disputed such a diagnosis. In this manner, by using multiple resources, it is believed that a nearly complete collection of clinically identifiable cases occurring in this city's population of 30.000 was achieved. Certain shortcomings in the use of survey data in a city of this size should be recognized; first of all, the data are not necessarily representative of other populations in the United States; secondly, the local population is small, and rates may be subject to appreciable chance fluctuation; thirdly, it would be difficult, for reasons mentioned, to match the completeness of this survey in other communities.

For the calculation of prevalence rates, patients must have been residents in the community for two years before January 1, 1955, and they had to have recognized symptoms before January 1, 1955. Determination of incidence was more difficult. Since symptoms often developed insidiously, the exact date of onset was not clear, and could not be ascertained from the records for 1/3 of the patients. However, if one can assume that new cases are occurring and being diagnosed at a steady rate in a population of fixed size, annual incidence rates based on the date of the first locally recorded diagnoses can be derived.

The 95 cases observed during the ten year period were classified into a) *symptomatic Parkinsonism* (44 cases), subdivided into the postencephalitic type (9 cases), Parkinsonism in the presence of recognized arteriosclerosis (35 cases), and cases related to known miscellaneous toxic or traumatic agents (0); and b) *idiopathic Parkinsonism*, without encephalitis, recognized arteriosclerosis or other identifiable precipitating cause (51 cases).

All 9 postencephalitic cases gave a clear history of encephalitis, an onset of Parkinsonism at about age 30 years, and no family history of a similar ailment. Of the 35 with Parkinsonism in association with arteriosclerosis, the onset was at an average of 70 years, and there was a family history of a similar condition in only 1. Of the 51 cases not associated with arteriosclerosis, etc., the average age of onset was 59 years, and in 16 percent there was history of Parkinsonism or a suspicious tremor in a close relative.

On the basis of the 71 cases who had their first local diagnosis recorded during the 10-year period of the study, 1945-54, it is estimated that each year about 1 person per 4.000 in the total population of the United States, and about 1 per 1.000 in the population aged 50 years and over are *newly* affected(10). For the United States population in 1960 this represents an incidence of about 36.000 new cases per year (95% confidence interval 27.000 to 45.000)*.

Few of the *new* cases in Rochester developing during the 10 year period of the study appear to be associated with encephalitis or with identifiable toxic agents. Most cases were classified as "associated with arteriosclerosis" or "without recognized associated conditions" (idiopathic). Arteriosclerosis is believed to have been coincidental rather than a causative factor in most instances.

The average age at onset recorded for the Rochester patients was about 67 years (more than 10 years later, on the average, than reported in recent clinical studies). This is believed to reflect in part the decreasing incidence of postencephalitic cases in recent years. However, the Rochester study is believed to be far more representative of the illness of the population of the community as a whole than are series of clinical or specialist cases which are believed to be biased in favor of younger patients.

There was no appreciable difference by sex in the ages of onset; the incidence and prevalence rates were only slightly greater

* If it can be assumed that the United States is randomly represented by the Rochester data, there are 19 chances in 20 (95% confidence interval) that the annual diagnostic incidence rate for Parkinsonism would be between 14.9 and 25.1 per 100.000 population and that between 27.000 and 45.000 patients could be newly diagnosed (and presumably at least this number are newly affected) each year.

for males than for females. The age specific incidence, prevalence and mortality rates were almost nil before age 50 years, rose gradually at age 60 years and increased sharply after 60 years of age.

About 2.5% of the population may be expected to develop Parkinsonism at some time during life(10). At any one time, the number of clinically identifiable cases is about 1.8 per thousand total population or nearly 1% for the population aged 50 years and over. For the United States as a whole in 1961, it is estimated that there are about 280.000 clinically identifiable cases (95% confidence interval 200.000 to 360.000 cases).

On the basis of the limited data available, it appears that death rates from all causes among patients with Parkinsonism are about 1/3 greater than death rates from all causes among the normal population of the same age distribution(10).

Genetic Considerations

Denny-Brown(11) states that "idiopathic Parkinsonism has a well defined hereditary liability, which has been estimated to be present in 4 to 15% in several large series of cases". Kinnier Wilson(12) states "little enough note has been taken, perhaps, of endogenous or intrinsic factors, among which heredofamilial disposition must be counted. A considerable number of familial cases are on record... heredity has been estimated... to be at about 15 percent, though this figure seems to me rather high". Among Rochester cases of Parkinsonism which were not associated with encephalitis or arteriosclerosis, 16 percent presented a history of a similar illness in other members of the family. Unfortunately, routine case histories were not adequate for genealogical analysis. In Mjones' extensive study(6) of 326 patients with paralysis agitans and Parkinsonism from clinics in Sweden, one or more secondary cases were reported in 19 percent of the "arteriosclerotic" Parkinsonism, in 41 percent of (idiopathic) paralysis agitans, and in 42 percent of the encephalitic cases. After an analysis of pedigrees of the 79 probands among the paralysis agitans group who showed secondary cases, Mjones concluded "with a high degree of probability, the mode of inheritance for paralysis agitans cases... is monohybrid autosomal dominance. The degree of manifestation (i.e., penetrance) is estimated to be approximately 60%". Only three probands among his paralysis agitans cases were twins, and all were probably dizygotic. No extensive analysis of twins with Parkinsonism has been carried out, although Schwab in Boston has begun a systematic collection of such cases(13).

William Allan(14) reported an interesting series of family studies in patients who were from the western half of North Carolina. In 62%, (45 of 72 consecutive cases) in which he could obtain an adequate family history, there was a similar disability in another member of the family. Detailed pedigrees with two to five generations of affected members were presented in one-third of his cases; these pedigrees included two Negro or partly Negro families. In one family there were said to be 42 affected persons, (24 males, 18 females) and the trait was thought to have descended through both men and women. Allan concluded that in about 2/3 of the cases he studied, "shaking palsy was inherited as a dominant trait, probably conditioned by a single autosomal gene". Allan also referred to a study by Bell and Clark(15) of a few selected sibships of affected parents in which half of the siblings who lived beyond 50 years of age were likewise affected. Mjones, in his review of Allan's paper, suggests that the material was collected with an over-representation of strongly affected persons, that there is insufficient description of the cases to ascertain that all the affected had paralysis agitans, and that Allan's inference regarding the mode of inheritance was not conclusive.

Among the more recent pedigree studies, Branger(16) has described a family of 28 belonging to four generations, in which he found 9 patients with definite signs of Parkinson's disease, and 2 with probable signs. The symptomatology and evolution of the disease were similar in the succeeding generations; the age of manifestation in all patients was between 48 and 53 years. There was no evidence of consanguinity in the

family, and Branger concluded that inheritance was by a dominant autosomal mechanism. In 1957, Pescetto(17) reported on a family of 26 members extending over 4 generations, of whom 13 were affected by typical Parkinsonism. He concluded a simple autosomal dominant gene was involved. Dastur, in 1956(18), reported 3 cases of Parkinsonism among 7 siblings whose parents were first cousins. The ages at onset were 48, 66, and 72 years, and there were no cases in the previous two generations.

There have been a number of reports of hereditary juvenile Parkinsonism(19). One of the more recent of these is the report by Ota, et al(20), of three cases among two sisters and one brother from 11 siblings. The parents of the propositi were first cousins, and the father had twin brothers who were said have had Parkinson's disease. The syndrome was unusual because it developed at a young age (12, 13 and 20 years) but there was no evidence of mental deterioration.

In the pedigrees presented by Dastur and Ota, the consanguinity of parents raises the question, but by no means proves, the role of a recessive mechanism. The similarity of the extrapyramidal symptoms alone should not be construed as evidence that these are all basically the same disease process; perhaps, as the biochemical nature of the various constituents of the Parkinsonism syndrome are identified, the relationship of these conditions to the bulk of cases will be clarified.

Parkinsonism-Dementia Complex on Guam

Genetic as well as epidemiological investigations are currently under way on Guam where a strange disease characterized by dementia and progressive extrapyramidal symptoms is endemic and accounts for about 7% of all deaths in adults(21, 22). The principal clinical features are mental deterioration of an organic type, akinesia and hyperreflexia. Tremor, rigidity, fixed faces, stooped posture, and other Parkinsonian features may be present; about 1/3 show definite evidence of upper or upper and lower motor involvement.

The mean age for the occurrence of Parkinsonism-dementia complex is 50 years, and almost all cases develop in the fifth and sixth decades of life. There is a preponderance of males, about 3 to 1. Death occurs from 3-5 years after onset, and is usually caused by inanition or aspiration pneumonia. Examination of 20 necropsied cases has shown no characteristic abnormality outside the nervous system, other than certain skin changes in collagen structure. There is gross cortical and pallidal atrophy, loss of pigment in the substantia nigra, and widespread degeneration of ganglion cells. There are numerous intraganglionic fibrillary changes and scattered intracytoplasmic granulovacuolar bodies, but there are no typical senile plaques, Pick's or Lewy's inclusion bodies. In a number of cases a close relationship between amytrophic lateral sclerosis and Parkinsonism-dementia complex of the Chamorros has been demonstrated, both by similarities of age, sex, and geographic distribution of the cases, by the duration of onset to death, by the family histories, and by pathological and clinical features. At the present, intensive work is under way to determine if a botanical toxic agent is important, and to collect pedigrees of patients on Guam and neighboring islands, to clarify the relative roles of exogenous and genetic factors.

Hereditary Factors in Drug Induced Parkinsonism

It has been noted that about 15% of patients with various disorders receiving the therapeutic phenothiazine derivatives, which were in vogue about 1958-60, in moderate or high doses, will develop symptoms of Parkinsonism within a few weeks. The symptoms of Parkinsonism disappear in these patients when the drug is withdrawn or the dose is reduced. It is not clear why some individuals are predisposed to develop Parkinsonian symptoms and why others are not, but a current study is under way at the National Institutes of Health, to determine whether there is an hereditary susceptibility. Hospital patients have been selected on the basis of whether they are susceptible (propositi) or resistant (controls) to Parkinsonism on high therapeutic levels of

ataraxic drugs. For both groups, genealogic investigations of Parkinsonism and related disorders will be carried out. Preliminary data indicate that relatives of patients who develop Parkinsonian symptoms on administration of ataraxic drugs have a higher frequency of Parkinson's disease than relatives of patients who do not develop Parkinsonian symptoms while on ataraxic drugs(23).

DISCUSSION

Parkinsonism is a syndrome in which numerous etiologic factors including genetic, infectious, vascular, and other mechanisms play a role. There are probably a number of distinct disease entities included in the syndrome, which will be identified as many research activities now under way reach fruition. The statistical data on Parkinsonism which have been presented may help to clarify the importance of some of the different etiologic hypotheses which others have proposed.

While mortality statistics for Parkinsonism are subject to considerable error, they have some value for broad geographic comparisons. The observation of relatively stable rates for the regions of the United States and for Canada suggest that the causative factor or factors are widely but fairly evenly distributed. Both mortality statistics and morbidity surveys described here indicate that there is slight selectivity for males. Whether this is due to some environmental exposure or to a sex chromosome association is still difficult to determine.

The Rochester, Minnesota, survey is believed to provide the most complete population statistics on Parkinsonism reported to date. Prevalence and incidence data from that source reveal that Parkinsonism is one of the most prevalent of the chronic neurologic disorders. The mean age at onset is over ten years later than that reported in clinical series of the past few decades. This can be explained in part by the absence in the present study of recent post-encephalitic cases which tend to occur at younger ages. Furthermore, the present study provides data which are believed to be far more representative of the disease impact on the community as a whole than are the earlier reports from specialists in which the younger patients with family responsibilities would tend to be overly represented.

The roster of cases developed in the Rochester study is based on clinical reports with a diagnosis of Parkinsonism or paralysis agitans. Patients with the diagnosis of essential, familial, or senile tremor were not included in the study; patients with these relative mild afflictions are likely to be under-reported in either community survey procedures or family histories, and no attempt was made to evaluate the association of these conditions with routine clinical histories which were available. Critchley(24) and Mjones(6) report that familial tremor is sometimes observed in families in which Parkinsonism has occurred. These writers suggest that in some instances familial tremor represents a "forme fruste" of the Parkinson syndrome. There is a possibility that familial tremor represents one segment of the spectrum of movement disorders including familial Parkinsonism.

One of the basic issues considered is the relative importance of exogenous and endogenous factors in Parkinsonism. It is difficult to accept the hypothesis of Schwab and associates, that the majority of idiopathic Parkinsonism is related to infection with the Von Economo influenza virus from 1917 to 1926, and that consequently, as the present cases of Parkinsonism who contracted their disease four decades ago die off, Parkinsonism itself will disappear(25). Lillie is said to have described the pathologic findings of a case from an encephalitis epidemic in 1942 as similar to cases of Von Economo encephalitis in the 1920's(26). Starkey suggests that this case may be an indication that Von Economo infection has not disappeared, although it may merely represent a general type of reaction to a similar virus(26). Haymaker points out that other encephalitides are not presently known to be followed by Parkinsonism; for example, Japanese B, Murray Valley, and Western Equine types(26). Ward has described two cases of transient Parkinsonism following Asian flu(26).

The importance of arteriosclerosis in Parkinsonism is equally difficult to determine.

Haymaker points out that in older age groups he has seen no difference in arterial walls in the brain between those with and those without the Parkinsonian syndrome; and that the appearance of vessels is hard to correlate with presence or absence of brain damage(26).

The extremely high prevalence of an unusual form of Parkinsonism on the island of Guam, and the studies to determine the roles of exogenous and genetic factors in the development of this disorder should, if successful, influence many aspects of Parkinsonism research.

One contribution of the Rochester study is to bring into proper focus presumed associations of Parkinsonism and other conditions. It appears that 2 to 3 percent of a population may be expected to develop Parkinsonism at some time after birth. This means that by chance, from time to time, either solitary cases of Parkinsonism, or several cases in a family (particularly where families are carefully studied) will appear in the presence of other disorders. In 16 percent of the Rochester cases of Parkinsonism which were not thought to be associated with encephalitis or arteriosclerosis, there was a history of a similar illness in other members of the family. The determination of the percentages of "positive family history" is not the preferred method of estimating familial susceptibility, and certainly in the retrospective study of clinical records in Rochester there is some question of the completeness of the analysis. Over the past twenty years there have been few systematic genealogical reports, and the outstanding ones at this time remain the studies by Allan(14) and by Mjones(6). In both of these, extensive pedigrees compatible with a dominant mode of inheritance were reported. In a number of their pedigrees, however, there were examples of skipped generations which would suggest that "penetrance" for the trait is not complete.

For an illness such as Parkinsonism with an appreciable spread in age of onset and frequently the very late manifestation of the disease, as demonstrated in the Rochester study, a hystory of a similar illness in relations will often be absent. Individuals of the appropriate genotype may have died before the age of manifestation of the disease, or such individuals may not have passed to the age of risk at the time of a genetic investigation. The statement of Gowers(27) in his discussion on paralysis agitans more than 60 years ago is still applicable: "In senile maladies the facts that can be ascertained regarding heredity probably fall short of the truth to a greater extent than in the maladies of earlier life, because, as life goes on, the death of older relations lessens the opportunity of ascertaining the facts. It is often astonishing how much disease inquiry sometimes reveals in the families of those who imagine, before inquiry is made, that they are absolutely free from all morbid heredity, so carefully have unpleasant facts been concealed by those to whom they are known".

Some physicians may not appreciate the time and effort required to obtain an accurate and detailed family history, even for an illness which is not often accepted as hereditary. The data reviewed here argue in favor of an important genetic mechanism in some, and perhaps most forms of Parkinsonism. The high percentage of positive family history for the postencephalitic and arteriosclerotic classifications in Mjones' study emphasized the need for further study of cases classified to these groups as well.

Summary and Conclusions

1. This review of epidemiologic studies of Parkinsonism includes an analysis of mortality statistics in the United States and Canada, a morbidity survey in Rochester, Minnesota, and an evaluation of several recent reports on possible etiologic mechanisms. The mortality statistics disclose a slightly higher mortality rate for males than for females. The mortality rates are similar in large regions of the United States and Canada. Deaths occurring in persons with Parkinsonism are believed to be underreported and make it difficult to use official mortality data for detailed geographic, racial, and other comparisons.

2. Incidence and prevalence rates for the resident population of Rochester, Minnesota, from case reports of the Mayo Cli-

nic and other sources of medical information in the community are several times higher than those reported from surveys in England and Sweden. However, the more complete case finding in the Rochester study is believed to be responsible for the difference rather than any true geographic variation.

3. The statistics for Rochester, Minnesota although believed to be minimal values, have been used to estimate incidence and prevalence for the United States; problems relating to such generalizations are reviewed. Each year, about 1 per 4.000 in the total population and about 1 in each 1.000 in the population age 50 years and over are newly affected. For the United States this represents an incidence of about 36.000 new cases per year. For the U.S. as a whole, it is estimated that there are at the present time about 280.000 clinically identifiable cases of Parkinsonism, making it one of the more serious neurological disorders with which the population is faced. In view of the increasing size of the population in the older age groups, it is likely that Parkinsonism will become an increasingly serious problem unless some preventive measures are found. Other populations of the world are probably also faced with similar risks.

4. Very few of the recent cases in the Rochester study appear to be associated with encephalitis or with identifiable toxic agents. The difficulty in classifying cases into those "with recognized arteriosclerosis" at onset of symptoms and those without any recognized associated conditions (idiopathic) was considered; the possibility that arteriosclerosis, when present, may be coincidental was discussed. The mean ages at onset for the group with recognized arteriosclerosis and the idiopathic groups are about 70 and 59 years respectively, but there is an appreciable overlap in the ages at onset. There is an interval of a few years, on the average, from onset of symptoms to the first local diagnosis of Parkinsonism.

5. The later average ages at onset (about 67 years) for all cases occurring 1945-1954, inclusive, when compared to earlier reports, is believed to be a reflection in part of the decreasing incidente of postencephalitic cases in recent years. Furthermore, the Rochester study is believed to be far more representative of the illness of the population of the community as a whole than are series of clinical or specialists' cases which have been reported. For the Rochester cases, there is no appreciable difference by sex in the ages at onset or of diagnosis.

6. The age specific incidence, prevalence and mortality rates increased sharply after 50 years of age. The incidence and prevalence rates in Rochester, Minnesota, are only slightly greater in males than in females.

7. On the basis of the limited data available, death rates among patients with Parkinsonism are about 1/3 greater than the death rates from all causes among the normal population of the same age distribution.

8. In Rochester, Minnesota, 16 per cent of the cases classified as idiopathic Parkinsonism gave a history of a similar illness in another member of the family. This is believed to be a minimal percentage and the disadvantages of evaluating heredity in a disease of unknown etiology through this method of "positive family history" have been reviewed. Several detailed genetic reports from other sources were described; these are believed to provide appreciable evidence that a high proportion of idiopathic Parkinsonism cases are inherited as a dominant trait with incomplete penetrance. In one report reviewed there is evidence that a predisposing hereditary factor might also be present in cases of encephalitic Parkinsonism.

9. Genetic and epidemiologic investigations are now underway on Guam where a strange neurological disease with dementia and progressive extrapyramidal symptoms is endemic and accounts for 7 percent of all adult deaths. It has been hypothesized that this disease may be genetically transmitted, but made manifest by an additional environmental factor such as a botanical toxic agent.

10. Studies of concordance for Parkin-

sonism in twins and of the possible constitutional factors in reactions to ataraxic compounds were suggested as steps in defining the relative roles of genetics and exogenous factors in the various forms of Parkinsonism.

RESUMEN

1. Esta revisión de los estudios epidemiológicos del Parkinsonismo incluye un análisis de las estadísticas de mortalidad en los Estados Unidos y Canadá. Una investigación acerca de la morbidez en Rochester, Minnesota, y una evaluación de varias comunicaciones recientes sobre posibles mecanismos etiológicos. Las estadísticas de mortalidad señalan una mortalidad levemente mayor en los hombres que en las mujeres.

Las cifras de mortalidad son similares en amplias regiones de los Estados Unidos y Canadá.

Se cree que los fallecimientos de Parkinsonismo no son siempre señalados como tales, lo cual hace difícil usar los datos oficiales de mortalidad para establecer comparaciones geográficas, raciales, etc.

2. El porcentaje de la incidencia y preponderancia en la población de Rochester, Minnesota, de casos recogidos de la Mayo Clínica y de otras fuentes de información médica de la comunidad, es varias veces más alto que aquellos comunicados después de estudios realizados en Inglaterra y en Suecia. Sin embargo es posible que la razón de esta diferencia esté en que la encuesta en Rochester sea más completa y no en una variante geográfica.

3. Las estadísticas para Rochester, Minnesota, aunque se cree que son de valor mínimo, han sido usadas para estimar la incidencia y preponderancia para los Estados Unidos. Se ha pasado revista a los problemas relacionados con tales generalizaciones. Cada año inician su enfermedad cerca de 1 por 4.000 en el total de la población y cerca de 1 en cada 1.000 en la población de 50 o más años de edad. Para los Estados Unidos esto representa una incidencia de cerca de 36.000 nuevos casos por año. Para los Estados Unidos en total se ha estimado que hay en el presente cerca de 280.000 casos clínicamente identificables de Parkinsonismo, considerándose éste uno de los más serios desórdenes neurológicos a los cuales la población se enfrenta. En vista del creciente tamaño de la población en el grupo de los ancianos, es muy factible que el Parkinsonismo se vuelva un problema cada vez más serio a menos que sean encontradas algunas medidas preventivas.

Otras poblaciones del mundo están probablemente también enfrentadas a riesgos similares.

4. Muy pocos de los recientes casos en el estudio de Rochester parecen estar asociados con encefalitis o con agentes tóxicos identificables.

Fue considerada la dificultad que existe para clasificar al comenzar los síntomas, unos casos dentro de aquéllos "con reconocida arterioesclerosis" y otros en el grupo del Parkinson idiopático. Se discutió la posibilidad de que la arterioesclerosis, cuando presente, pueda ser sólo una coincidencia.

El promedio de edad del comienzo para el grupo con reconocida arterioesclerosis y el grupo idiopático es de alrededor de 70 y 59 años respectivamente, pero hay muchos casos en que el comienzo se hace a edades iguales. Por lo general hay un intervalo de unos pocos años, desde la aparición de los síntomas al primer diagnóstico de Parkinsonismo.

5. La diferencia en el término medio de la edad de comienzo de la enfermedad (cerca de 67 años) para los casos ocurridos de 1945 a 1954 inclusive, cuando se compara con la que demuestran estudios anteriormente hechos, se cree que es en parte el reflejo del decrecimiento de los casos postencefalíticos en los últimos años. Además se piensa que el estudio de Rochester sea mucho más representativo de la enfermedad en una comunidad, que lo que se desprende de las publicaciones de series de casos hechos por clínicos o especialistas.

Para los casos de Rochester, no hay apreciable diferencia en los sexos en lo que se refiere a la edad de la aparición de los síntomas o del diagnóstico.

6. La proporción de incidencia, predominio y mortalidad aumentan rápidamente

después de los 50 años de edad. Las cifras de incidencia y predominio en Rochester, Minnesota, son ligeramente más elevadas en los hombres que en las mujeres.

7. En base a los limitados datos disponibles, los índices de mortalidad entre los pacientes con Parkinsonismo son aproximadamente 1/3 más grandes que los índices de mortalidad debidos a todas las causas entre la población normal de edades semejantes.

8. En Rochester, Minnesota, el 16 por ciento de los casos clasificados como Parkinsonismo idiopático dieron una historia de enfermedad similar en otro miembro de la familia. Se piensa que esto es un porcentaje mínimo y se consideran las desventajas de avaluar la herencia en una enfermedad de etiología desconocida por este método de "historia familiar positiva".

Se describieron varias comunicaciones de otras fuentes sobre genética; se cree que estas aportan apreciable evidencia de que una alta proporción de Parkinsonismos idiopáticos son heredados como un rasgo dominante con penetración incompleta.

En una de las comunicaciones citadas hay evidencia de que una predisposición hereditaria, podría también estar presente en casos de Parkinsonismo postencefalítico.

9. Investigaciones genéticas y epidemiológicas están ahora en camino en Guam donde una extraña enfermedad neurológica con demencia y síntomas progresivos extrapiramidales es endémica y da cuenta del 7 por ciento de todas las muertes en adultos. Se ha formulado la hipótesis de que esta enfermedad puede ser genéticamente trasmitida, pero se hace manifiesta merced a un factor ambiental adicional tal como un agente botánico tóxico.

10. Estudios de la concordancia del Parkinsonismo en mellizos y de los posibles factores constitucionales en las reacciones a los compuestos ataráxicos, fueron sugeridos como elementos para definir la importancia relativa de los factores genéticos y exógenos en las distintas formas de Parkinsonismo.

RESUME

1. Cette revision des études epidémiologiques du Parkinsonism inclus une analyse des statistiques de mortalité aux Etats Unis et au Canada, une recherche au sujet de la morbidesse en Rochester Minnesota et une évaluation de plusieurs communications récentes sur possibles mécanismes étiologiques. Les statistiques de mortalité indiquent une petite différence de mortalité, plus grande chez les hommes que chez les femmes.

Les chiffres de mortalité sont similaires dans les grandes regions des Etats Unis et Canada.

On croit que les morts des personnes souffrant de Parkinsonism ne sont pas toutes rapportées ce qui rend difficile de donner des renseignements officiels de mortalité pour des comparaisons géographiques ratiales, etc.

2. La proportion de l'incidence et prépondérance pour la population résidant en Rochester, Minnesota, des cas communiqués par la Mayo Clinic et d'autres source d'information médicales dans la communauté est plusieurs fois plus élevées que celles communiquées des études realisées en Angleterre et Suède. Cependant une plus complete investigation au sujet des cas, dans l'étude de Rochester peut être que ce soit la responsable de la différence, plus qu'une véritable variation geógraphique.

3. Les statistiques pour Rochester, Minnesota quoique on les croit être de valeur minime ont été employées pour estimer l'incidence et la préponderance aux Etats Unis; des problèmes relationnés à ces généralisations sont revisées.

Chaque année, près de 1 dans chaque 4.000 en total de la population et près de 1 dans chaque 1.000 dans la population de 50 ans et plus âgée sont affectés.

Pour les Etats Unis ceci représente une incidence de 36.000 de nouveaux cas par année, pour les Etats Unis en total on a estimé qu'il y a dans le présent près de 280.000 cas cliniquement indentifies de Parkinsonism, considerant cet maladie un des plus sérieux désordre neurologique, auquel font face la population. En considerant l'augmentation incessante de la population

dans le groupe des veillards c'est très factible que le Parkinsonism devienne un problème sérieux en augmentant, à moins que quelques mesures préventives soient trouvées. Probablement d'autres populations du monde font face à des risques similaires.

4. Très peu des cas récents étudiées en Rochester semblent être associés avec l'encéphalite au avec des agents toxiques identifiés.

La difficulté de classifier des cas dans ceux "avec arterioclerose reconnus" au commencement des symptômes et ceux sans aucune condition associée reconnue (idiopathique) a été considerée, la possibilité que l'arteriosclerose quand elle est présente, peut être dû à une coincidence a été discutée. Généralment l'âge du commencement pour des groupes d'arterioscleroses reconnus et dans les groupes idiopathiques sont de 70 et 59 ans respectivement, mais il y a une appréciable superposition des âges dans le commencement.

Quelques fois il y a un intervale de peu d'années depuis l'apparition des symptômes et le diagnostique du Parkinson.

5. La moyenne des âges plus avancées pour le commencement de la maladie (près de 67 ans) dans tous les cas arrivés en 1945-1954 inclus, quand on la compare avec des études faites antérieurement on croit que ce sont en partie un reflet de la decroissante incidence de cas post encephalitic dans les années récents. Plus encore l'étude de Rochester semble être plus representative de la maladie de la population d'une communauté totale, plus qu'une serie de cas communiqués par des cliniciens ou des spécialistes.

Pour les cas de Rochester il n'y a pas de différence appreciable quant au sexe, dans l'âge de l'initiation ou du diagnostique de la maladie.

La statistique de l'âge de l'incidence, predominance et mortalité augmentent rapidemant après les 50 ans. Les chifres d'incidence et prédominance en Rochester Minnesota sont un peu plus élevés chez des hommes.

7. En base aux renseignements limités disponibles, les chiffres de mortalité entre les patients avec le Parkinson son près de 1/3 pour cent, plus grands que les chifres de mortalité dû à toutes les autres causes parmi la population normale dans la méme distribution d'âge.

8. En Rochester, Minnesota le 16 % des cas classifiés comme Parkinson idiopathique donne une histoire de maladies similaires dans d'autres membres de la famille.

On croit qu'il est un pourcentage minime et elles on été etudiées les desadvantages de valorer l'héritage dans cette maladie d'origine incomune à travers de cette méthode "d'histoire familiale positive". Plusieurs rapports génétiques détaillés de d'autres sources ont été décrits, ont croit que ceci apportent une apréciable évidence, qu'une haute proportion de Parkinson idiopathique a una qualité héreditaire dominante avec una penetration incomplete. Dans une des rapport etudié il y a évidence d'une prédisposition héréditaire facteur qui pourrait aussi être présent dans le cas de Parkinson encephalitic.

9. Des investigations génétiques et épidémiques sont maintenant en étude en Guam où une étrange maladie néurologique avec démence et des symptômes progressifs extrapyramidales est endémique et cause le 7 % de toutes les morts arrivées dans l'âge adulte.

On a dejá posé l'hypothèse que cette maladie peut être génétiquement transmises mais elle s'est fait évidente grâce à un facteur régional additionnele tel qu'un agent botanique toxique.

Etudes de la concordance du Parkinsonism dans les jumeaux et des facteurs possibles constitutiònels dans les réactions aux composée ataraxiques peuvent être utils pour définir les rôles relatifs aux facteurs génétiques et exogenes dans les differentes formes du Parkinsonism.

ZUSAMMENFASSUNG

1. Die epidemiologischen Studien der Parkinsonschen Krankheit ergeben eine Analyse der Mortalitaetsstatistik in den U.S.A. und Canada, einen Ueberblik ueber die Morbiditaet in Rochester und eine Auswertung von verschiedenen modernen Publikationen ueber die Aetiologie der Krankheit. Die Mortalitaetsstatistik ergibt eine leicht

hoehere Mortalitaet fuer Maenner als fuer Frauen. Die Mortalitaet ist aehnlich in grossen Gebieten der U.S.A. und Canada. Todesfaelle durch Parkinson werden wahrscheinlich zu wenig gemeldet, und es ist deshalb schwierig, die offiziellen Mortalitaetsziffern zu verwenden, um die geographische oder rassische Verteilung der Krankheit zu beurteilen.

2. Die Haeufigkeit des Parkinson in der Bevoelkerung von Rochester, beurteilt nach Informationen der Mayo Klinik und anderen Quellen, ist viel hoeher als diejenige in England und Schweden. Es ist jedoch anzunehmen, dass die genaueren Krankengeschichten von Rochester verantwortlich sind fuer diesen Unterschied eher als eine wirkliche geographische Variation.

3. Die Statistik von Rochester wurde verwendet, um die Haeufigkeit der Krankheit in den U.S.A. zu schaetzen. Jedes Jahr tritt ein neuer Fall auf unter 4 000 Menschen und ein Fall unter tausend Menschen von 50 Jahren und darueber. Das ergibt fuer die U.S.A. ungefaehr 36.000 neue Faelle von Parkinson pro Jahr. Man schaetzt die totale Zahl von Patienten in U.S.A. auf ungefaehr 280.000, sodass die Krankheit als eine der ziemlich ersten neurologischen Stoerungen zu betrachten ist. In Anbetracht der Zunahme der hoeheren Altersgruppen ist es wahrscheinlich, dass der Parkinson ein immer ernsteres Problem darstellen wird, wenn nicht praeventive Massnahmen gefunden werden koennen. Die Bevoelkerungen anderer Laender sind wahrscheinlich einer aehnlichen Gefahr ausgesetzt.

4. Sehr wenige der in Rochester kuerzlich diagnostizierten Faelle scheinen assoziiert zu sein mit Encephalitis oder mit toxisch wirkenden Substanzen. Es ist schwierig, die Faelle einzuteilen in solche "mit klarer Arteriosklerose" beim Beginn der Symptome und in solche ohne irgendwelche Begleitsymptome (idiopatischer P.) Es wird die Moeglichkeit in Betracht gezogen, dass die Arteriosklerose, wenn sie vorhanden ist, zufaellig gleichzeitig aufgetreten ist. Das Durchschnittsalter der Patienten mit Arteriosklerose ist 70 Jahre, und dasjenige der idiopatischen Gruppe 59 Jahre. Aber es besteht ein betraechtliches Ueberschneiden des Alters beim Beginn der Krankheit. Das Intervall zwischen dem Ausbruch der Symptome und der Diagnose des Parkinson ist meist einige Jahre.

5. Das hoehere Durchschnittsalter (ungefaehr 67 Jahre) fuer alle Faelle, die zwischen 1945 und 1954 aufgetreten sind, scheint bedingt zu sein durch die immer kleiner werdende Haeufigkeit der postencephalitischen Faelle in den letzten Jahren. Bei den in Rochester gefundenen Faellen besteht kein sicherer Unterschied zwischen beiden Geschlechtern beim Beginn der Krankheit.

6. Die fuer das Alter spezifische Haeufigkeit und die Mortalitaet nehmen rasch zu beim Alter ueber 50. In Rochester tritt die Krankheit nur wenig haeufiger auf bei Maennern als bei Frauen.

7. Die Mortalitaet der Parkinson-Patienten ist ungefaehr ein drittel höher als diejenige der normalen Bevoelkerung desselben Alters.

8. In Rochester findet man bei 16 % der als idiopathischer Parkinson klassifizierten Faelle eine aehnliche Krankheit bei andern Familienmitgliedern. Es werden verschiedene Publikationen erwaehnt, in welchen genaue Familiengeschichten beschrieben werden. Diese scheinen anzudeuten, dass ein hoher Prozentsatz der Faelle von idiopathischem Parkinson in dominanter Weise vererbt wird. Eine Publikation zeigt, dass ein praedisponierender hereditaerer Faktor auch beim encephalitischen Parkinson orhanden sein koennte.

9. Genetische und epidemiologische Studien werden zur Zeit in Guam durchgefuehrt, wo eine merkwuerdige neurologische Krankheit mit Demenz und progressiven extrapyramidalen Stoerungen endemisch ist und verantwortlich ist fuer 7 % aller Todesfaelle unter Erwachsenen. Es wurde die Hypothese aufgestellt, dass diese Krankheit erblich uebertragen wird, aber erst manifest wird durch einen zusaetzlichen Faktor wie z.B. ein pflanzliches Toxin.

10. Untersuchungen ueber das Auftreten von Parkinson bei Zwillingen und ueber eventuelle konstitutionelle Faktoren bei den Reaktionen auf ataraxische Substanzen werden erwaehnt als moegliche Schritte in der Aufklaerung des Einflusses der genetischen und exogenen Faktoren bei den verschiedenen Formen des Parkinson.

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The Pallidal Lesion of Parkinsonism

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Though parkinsonism is a condition that presents little difficulty in diagnosis, analysis of its symptomatology and pathology has intrigued and baffled neurologists for more than a hundred years. The first and greatest difficulty is that the normal functions that are disturbed have never been satisfactorily defined. The pathology of the disease is diffuse, the causes multiple, and the symptomcomplex has not been reproducible experimentally. Yet it is possible to approach this problem by an analysis of other disorders of the basal ganglia, and this we have done at some length in the Croonian Lectures, given in London in February 1960. These will ultimately be published in monograph form, and a brief account has already appeared(6).

Description of the symptomatology of paralysis agitans is commonly reduced to terms of a specific tremor with rigidity of plastic type. A more ample description would have to include bradykinesia, for this symptom is not always fully accounted for by the degree of rigidity, and compulsive movements or postures that are sometimes more evident than tremor. In addition the descriptions in our modern textbooks often totally neglect to mention the very characteristic change in posture that interested Charcot and Brissaud, and was discussed at some length by Bechet(2) and by Richer and Meige(25). The progressive change in the posture of the hand has been compared to that of rheumatoid arthritis(23), owing to the intense overflexion of the metacarpophalangeal joints, with extension of the fingers. A gradual assumption of flexed posture of the upper limbs, later of lower limbs, is associated with increasing flexion of wrists and metacarpophalangeal joints, and plantar flexion of the ankles. In the terminal stage the patient lies flexed at all joints except the ankles and fingers, which are extended. As this state, which we call flexion dystonia, develops, the tremor is lessened, and may disappear. The plastic feature of rigidity is gradually replaced by a progressive type of resistance of the muscles to stretch, that was called contracture by the older writers. It is not contracture in the sense of a fixed muscular or tendinous length, for the posture can still be modified by various manipulations, or by nerve block. Electromyographic study shows that this resistance is a progressive stretch reflex, lacking the "lengthening reaction" that characterises spasticity, and no longer showing the dropping-out and coming-in (alternation) of motor units that characterises plastic rigidity(6, 8).

If the gradual development of flexion dystonia in paralysis agitans is viewed in this way, its relation to the effect of more gross lesions of globus pallidus becomes evident. The clinical state that best exemplifies this is that resulting from severe carbon monoxide poisoning. When the cortical and subcortical lesions of that condition are mild, and pallidal necrosis severe, a condition of general flexion with akinesia results. There is resistance to passive extension, mutism, absence of reflex grasping and sucking, and the eyes are open but staring. The same state can be reproduced by severe destruction of the inner globus pallidus in the monkey by electrolytic lesion(6), and has been described in the monkey following carbon disulfide intoxication(26).

Post-encephalitic parkinsonism differs greatly from paralysis agitans in re-

lation to the development and distribution of dystonia. The abnormal attitudes of post-encephalitics are more prominent from their beginning, and more frequently grossly asymmetrical. Asymmetry of the neck more commonly assumes the aspect of torticollis, the open-mouthed staring expression of the face develops earlier, and one or other arm is either intensely flexed and pronated, or extended and retracted. The lower limbs are more commonly stiffly extended. The rigidity, though plastic in the beginning, more rapidly develops a progressive resistance to stretch of the muscles that determine the abnormal attitude. We call this general pattern of flexed upper limbs, and extended lower limbs hemiplegic dystonia. Bradykinesia or akinesia are similar to that of paralysis agitans. In both diseases an emotional stimulus of strong visual context can enable a rapid movement, or clarity of speech, that is not possible under other circumstances, the "kinésie paradoxale" of Souques(27) and Babinski *et al*(1). Yet the basic dystonia is altogether different in post-encephalitic parkinsonism. It is identical with that resulting from progressive lesions as in dystonia musculorum deformans, or in Wilson's disease. The same hemiplegic dystonia also appears in the late stage of Huntington's Chorea, when the putamen as well as the caudate nucleus begins to show progressive atrophy. In all these states the rigidity is greatly increased when the patient is suspended in air by support under the arms. When he is lying on a flat surface the pattern of dystonia alters, from flexion when lying on one side, to more extended postures when lying on the back. The extreme development of hemiplegic dystonia occurs when bilateral necrosis of the putamen and caudate nucleus has occurred, as in the remarkable case of Marinesco and Draganesco(21). In this case the child lay flexed when on a surface and extremely rigidly extended in hemiplegic dystonia when suspended in the air.

We conclude therefore that the fundamental progressive disorder in paralysis agitans presents the dystonic change of progressive pallidal lesion, and that of post-encephalitic parkinsonism the dystonia of lesion of putamen. Arteriosclerotic parkinsonism also presents the hemiplegic dystonia of striatal lesion, commonly with more intense dystonia in one or other part (a dystonic foot response, or dystonic grasp).

Neuropathology

Pallor of the globus pallidus, in sections stained for myelin, with or without pallor of the ansa lenticularis, has been the most obvious and most commoly described lesion in parkinsonism since Jelgersma(17) and Lewy(19) first drew attention to the histological changes of this condition. Following the description of the lesions of the substantia nigra by Trétiakoff(28) these have gradually assumed greater prominence in pathogenesis. The careful charting of nigral lesions by Hassler(15) and his finding of them in all cases of paralysis agitans examined by him have convinced many that these are the essential lesions of parkinsonism. The most recent descriptions of the pathology have tended either to belittle the importance of pallidal lesions(13) or to omit them altogether(14). Yet it seems to be forgotten that severe destruction of the substantia nigra, with lesions in the locus coeruleus, were frequently found in cases of acute encephalitis lethargica without evidence of parkinsonism(16, 18, 22). The discrepancy has by some been explained by the delay in appearance of parkinsonian symptoms following its essential lesion, as in carbon monoxide poisoning for example. We ourselves are convinced that the delayed symptomatalogy of carbon monoxide poisoning is due to extension of damage to the walls of blood vessels, which become calcified around this type of lesion. There is certainly no delay in appearance of dystonia following electrolytic lesions in the monkey. We have found recent partial necrosis of the globus pallidus bilaterally, without nigral lesion, in an elderly man who developed parkinsonism three weeks before death. Lhermitte and Cornil(20) cite a similar case. Finally, we have chronic post-encephalitic brains with severe destruction of substantia nigra where tremor has not been a symptom, though striatal hemiplegic dystonia has been severe.

It is true that the cellular changes in the

globus pallidus and putamen in parkinsonism are often mild and indistinguishable from those of simple senility. In other cases they may be severe. This discrepancy has been noted in all pathological descriptions. The account of Foix and Nicolesco(11) coincides precisely with our own experience. We would emphasize the common finding of "paravascular degeneration" in the outer segment of globus pallidus in cases of paralysis agitans, and its extension to include the putamen in arteriosclerotic parkinsonism as described in greater detail by Foix and Nicolesco(10). When more obvious lacunes are present in the putamen the clinical state has presented more or less of pseudobulbar symptomatology than occurs with the precriblé state.

It is when one seeks the cause of the pallor of the globus pallidus that the true explanation becomes apparent. The pallor is due to loss of the dense network of finely myelinated fibers and neuropil that are characteristic of globus pallidus. It is even more evident in sections stained for axis cylinders than in those stained for myelin. In paralysis agitans it is due to damage to these fine fibers around the smallest blood vessels in irregular areas of the globus pallidus. As many others have noted there is commonly also some degree of siderosis, or of ferrocalcinous concretions, but these are not an essential part of the lesion. This "paravascular degeneration" is also found occasionally in general metabolic disorders such as Wilson's disease, Hallervorden-Spatz syndrome, and hypoparathyroidism, all of which can cause parkinsonism. The common feature in all these states is a breakdown of the blood-brain barrier in the capillaries of the globus pallidus, and less frequently in substantia nigra and dentate nucleus.

In post-encephalitic parkinsonism, and also in familial parkinsonism, the pallor of globus pallidus is more even, and is related to great reduction in number of strio-pallidal fibres. The bundles entering the globus pallidus from putamen are normally pale in myelin stains, owing to their content of a large number of very fine fibers. In these conditions the fine fibers are lost, particularly in bundles from the middle and posterior segments of putamen. In familial parkinsonism and in Huntington's Chorea the same loss of strio-pallidal fibers is also present, and there is intense gliosis of the outer putamen. In post-encephalitic parkinsonism this gliosis is more intense in the posterior half of putamen and in the external capsule, where there is a severe loss of cortico-striate fibers.

We are therefore convinced that the neuropathology of parkinsonism is more adequately explained by loss of nerve fibers than by loss of nerve cells. In paralysis agitans the loss appears to be in the terminal synaptic structure of the globus pallidus, long preceding loss of pallidal neurones. In post-encephalitic and similar states loss of cortico-striate fibers is presumably secondary to widespread loss and alternation of cortical neurones (Hallervorden 14). The functional significance of the lesion of substantia nigra remains to be determined, though our own impression reinforces that of von Economo(9) that it is chiefly concerned in the compulsive movements of mandibular and accessory respiratory musculature.

Physiological Aspects

Electromyographic analysis of parkinsonian rigidity reveals that it is primarily proprioceptive in origin. The muscles exhibit extremely sensitive stretch reflexes, so that after a preliminary relaxation a small movement in either direction at any joint sets up a reflex response(8). The plastic quality of resistance to passive movement is due to a lengthening reaction in each unit, causing motor units to cease discharge, then begin again, as stretch continues. If the stretch is made rapidly a large number of motor units may cease discharge together and at this moment the antagonistic muscle shows a burst of discharge ("shortening reaction"). The prominence of this reaction in antagonists is the "paradoxical contraction" of Westphal(30), the "tonic postural reflex" of Foix and Thévenard(12). It is seen in the dorsiflexors of the wrist and ankle when these joints are suddenly dorsiflexed, and is found at an intermediate stage in the development of dystonia. It is abolished by procain block of the motor

point of the stretched muscle, which shows that the proprioceptive reflexes take origin in the stretched muscle and excite both it and its antagonist in succession. When tremor is present it can be demonstrated to be a rhythmical series of paradoxical reactions.

An additional feature of the altered stretch reflexes is that they excite not only the muscle that is stimulated by stretching but synergists at the same and related joints. If the motor point of a muscle is blocked by procain these proprioceptive reflexes can no longer be obtained from that muscle, though the paradoxical reactions and tremor can still spread to it from other muscles. This is the explanation of the observation of Walshe(29) that procain can block rigidity but not tremor. Pollock and Davis(24) observed that surgical deafferentation of a limb of a post-encephalitic parkinsonian patient abolished the usual rigidity and tremor and left only a posture determined by labyrinth and neck posture. This also demonstrates that the pattern of dystonia is labyrinthine in part. As we have described above, the development of hemiplegic dystonia in such patients is associated with gradual loss of plastic reactions and their replacement by postures that are determined by position of the head and body in space.

To determine the meaning of the conflict of enhanced proprioceptive reactions in such patients we must turn to consideration of the cortical mechanisms that normally control proprioceptive responses. The tactile grasp reflex released by frontal lobe lesions, and the tactile avoiding response released by parietal lobe lesions are such responses(5). In these reactions a tactile stimulus "triggers" a proprioceptive reaction that then continues for a time without further tactile stimulus. The more extensive the cortical lesion the more widespread is the associated proprioceptive reaction(5), and the less restricted is the stimulus necessary to elicit it. This is "tonic innervation", as seen in the tonic grasp reflex and tonic foot response. Similar tonic deviation of the head and eyes is occasionally seen as a result of extensive occipital lesions. In monkey experiments we have presented evidence that these tonic tactile responses are associated with enhancement of body-contact righting reactions ("catatonic rigidity"), and the corresponding tonic optic responses with overactive labyrinthine reactions(7). It was deduced that the specialized cortical reactions are themselves modifications of lower level contact and labyrinthine righting reactions.

When athetosis is present as a result of lesion of putamen the abnormal movements can be shown to be determined by reaction to stimulation. The reflex effects are always a conflict of tonic grasping and avoiding, with preponderance of one or other. We have found that the putamen is the locus of subcortical integration of these responses. When the putamen is destroyed neither grasping nor avoiding, nor the corresponding optic reactions, can be elicited. In their place is a conflict between diffuse body contact and labyrinthine righting reactions. This is the explanation of the change in posture depending on whether the patient is lying on a surface or is suspended in air. The corresponding condition is reproducible in the monkey by lesion of the outer globus pallidus or by severe destruction of putamen. Labyrinthine tonic extension of the limbs when the animal is suspended, and righting in a free fall, are still obtainable. When the inner globus pallidus is destroyed there is loss of the tonic postures that are produced by change of position of the head and neck in space, absence of labyrinthine righting in a free fall, and now all body contact with surfaces leads to intense flexion of the limbs. The tonic labyrinthine postures require a reflex arc that depends on the integrity of the thalamopallidal fibers from the intralaminar nucleus that cross the internal capsule to enter the internal medullary lamina of the globus pallidus.

Though in the past overactivity of thalamic righting reflexes has often been suspected to be the basis for striatal dystonia, it has not been appreciated that there is a conflict of reactions, or that body contacts are important. Further each reaction is diffuse and extremely long lasting, so that the usual labyrinthine tests give unconvincing results. The modification of the abnormal postures of dystonia by alternation of

the position of the head while the patient is standing, or suspended by the arms, can however be regularly obtained, as also the change in postures when lying on the side or back on a flat surface. The latent period of reaction may be as long as one minute, and once elicited it may persist for five minutes.

Parkinsonian tremor is the most difficult response to analyse, for it has not been reproducible by any experimental lesion. We have two observations to contribute. First, in some cases of juvenile type of Wilson's disease, athetosis may, in the course of some weeks, gradually become more rapid and rhythmical, with less amplitude of movement. The change from overextension of fingers and thumb to flexion of fingers over the strongly adducted thumb becomes less complete so that the opposed thumb eventually beats rhythmically against the first finger in typical parkinsonian tremor(4). The conflict between grasping and avoiding that constitutes athetosis has then become rhythmically resolved as tremor. Secondly, in some cases of arteriosclerotic parkinsonism without tremor, it is possible to elicit 3 to 10 beats of parkinsonian tremor by concurrently stimulating both the dorsal and palmar surfaces of the hand. The simplest way to perform this maneuver is for the examiner to draw his hands over the hand of the patient, making a distally moving contact on both the dorsal and ventral surfaces of the patient's hand. In this way we are convinced that parkinsonian tremor represents a more intense conflict of the same factors in control of movement that are disturbed by lesions of the striatum. A diffuse lesion of the fiber systems of the globus pallidus is evidently necessary for its occurrence, for necrotizing focal lesions produce only dystonia.

Akinesia

We have presented very briefly some of our observations on parkinsonism. These abnormal reactions all relate to disturbance of the mechanisms of control of types of movement that are projected into the environment, determined and directed by exteroceptive stimuli such as contact and visión. In the past the pyramidal systems has been assumed to be the pathway for this type of movement and the extrapyramidal system for "automatic" or postural function. The cessation of parkinsonian tremor when hemiplegia affects the limb has been argued to mean that such tremor is a disorder of the function of the pyramidal system(31). Our findings indicate that this is a fallacy. The pyramidal system may be intact, yet akinesia be complete, in the presence of pallidal or striatal necrosis. Further, in the monkey the essential conditions for akinesia, release of body contact reactions and absence of labyrinthine reactions, can be produced by bilateral parietal cortex ablation followed by section of both 8th nerves. Flexion dystonia with absolute akinesia then occurs (Denny-Brown and Chambers, 7) though the precentral pyramidal system, frontal cortex, and basal ganglia remain intact. The earlier ideas of "centers" for voluntary movement, for posture, or for tremor must be discarded. In their place we introduce new concepts of the elaboration by the brain of the reflex factors that are the essential substrate of all motor behavior. The highly specialized type of projected motor reaction that is served by the pyramidal tract must be based on the reactions served by the basal ganglia.

It has long been noted that akinesia and bradykinesia in parkinsonism is not directly related to the degree of rigidity(31). Our observations indicate that these symptoms result from the loss of reflex facilitatory factors in movement, evident as a result of both pallidal and striatal lesions, and independent of the degree and type of release of lower level mechanism. It has nevertheless been possible to ameliorate abnormal conflicts of reflex factors by surgical lesions of outer globus pallidus. Our observations indicate that the beneficial effects of such operations result from the lessened afferent input from the tonic labyrinthine reactions. The danger of extension of lesion to inner globus pallidus with resulting mute, akinetic state has made it preferable to induce demage to the ventrolateral thalamus in such cases(3).

At the beginning we mentioned the cardinal symptoms of parkinsonism. From our

analysis of the syndrome it is concluded that it forms a spectrum of disorders. Akinesia and plastic rigidity are identical in type as a result of pallidal and striatal lesions, though the pattern of rigidity and the postural reactions differ greatly. The disturbance of speech is of the same type in both. If complete mutism is rarely the result of striatal lesions it is only because such lesions are rarely complete. Similarly the typical parkinsonian tremor rarely results from striatal lesion, though fragmentary tremors of irregular amplitude and rhythm, yet with characteristic opposition of thumb, occasionally occur. More commonly tonic grasp, tonic foot response, or tonic deviation of the eyes ("oculogyric crises") betray the instability of cortico-striate mechanisms that are associated with lesions that are primarily striatal in origin, yet present the classical immobility of parkinsonism. "Kinésie paradoxale" likewise reveals the presence of partially ineffective reflex mechanisms that can be facilitated by visual or tactile reinforcement. Our hypothesis of equilibria of competing physiological reactions at cortical level, disturbance of which leads to apraxia(5), is now seen to apply to the several levels of integration within the neuraxis. The involuntary movements and postures of parkinsonism represent the disequilibration of competing reflex factors at pallidal level.

Paralysis agitans remains the prototype of pallidal lesion. Its extremely slow progression causes the characteristic plastic rigidity and classical tremor to be present for long periods of time, and by these it is universally recognised. This phase is nevertheless only part of a sequence of change. Its terminal state of flexion dystonia is its most distinctive characteristic. The senile "paraplegia-in-flexion" of Yakovlev (32) is equally distinctive. Familial and "juvenile" parkinsonism belong to the more heterogeneous group of striatal types of parkinsonism though in these too the globus pallidus may in the end become severely damaged.

SUMMARY

It has not been sufficiently appreciated that the plastic rigidity of paralysis agitans gradually becomes more resistant to stretch in flexor muscle groups resulting in a terminal fixed posture in flexion (flexion dystonia). The change is due to the loss of the "lengthening reaction". This terminal state of flexion dystonia is that produced by necrosis of the globus pallidus in carbon monoxide poisoning. In post-encephalitic, arteriosclerotic and familial parkinsonism the same change occurs, but the terminal posture is one of hemiplegic dystonia (flexed upper limbs and extended lower limbs). This type of dystonia is produced by gross lesions of the putamen. A diffuse loss of the fiber systems of globus pallidus itself, or of striopallidal systems produces parkinsonism.

Loss of nerve cells is inconspicuous until late stages. The common lesion is the paravascular degeneration of Foix and Nicolesco. In post-encephalitic parkinsonism diffuse loss of cortico-striate and strio-pallidal fibers occurs, as part of widespread cell damage. The substantia nigra appears to be more concerned in bulbar coordination. Loss of cortico-striate fibers leads first to athetosis which is a conflict of tonic grasping and tonic avoiding responses. In Wilson's Disease athetosis may make gradual transition into parkinsonian tremor, which is viewed as a more intense conflict of the same tonic reflex factors.

As these disintegrate the labyrinthine righting reaction is released, resulting in hemiplegic dystonia. This reaction requires intact thalamo-pallidal fibers. Interruption of these fibers by surgery lessens the dystonia and the conflict of reactions. The conditions of flexion dystonia results from loss of both thalamo-pallidal fibers and strio-pallidal fibers, and is due to overactive body contact righting reactions. The associated akinesia is due to the loss of cortical and reflex factors in movement.

RESUMEN

No ha sido suficientemente apreciado que la rigidez plástica de la parálisis agitante gradualmente se hace más resistente al estiramiento en los grupos de músculos flexores, lo que resulta en una postura terminal fijada en flexión (distonía en flexión). El cambio es debido a la pérdida de la "reacción de alargamiento".

Este estado terminal de distonía en flexión es aquel producido por la necrosis del globus pallidus en el envenenamiento con monóxido de carbono. En el parkinsonismo familiar, arterioesclerótico y post-encefalítico ocurren los mismos cambios; pero la postura terminal es de distonía hemipléjica (miembros superiores flexionados e inferiores extendidos). Este tipo de distonía es producido por grandes lesiones del putamen. Una pérdida difusa de los sistemas de fibras del globus pallidus mismo o de los sistemas estrio-palidales produce parkinsonismo. La pérdida de células nerviosas no tienen significación hasta estados tardíos.

La lesión común es la degeneración paravascular de Foix y Nicolesco. En el parkinsonismo post encefalítico existe una pérdida difusa de fibras córtico estriadas y estriopalidales, como parte de un daño celular más extenso. La sustancia nigra aparece más en relación con la coordinación bulbar. La pérdida de las fibras corticoestriadas conduce primero a la atetosis, la cual es un conflicto de respuestas tónicas de prehensión y de retirada. En la enfermedad de Wilson la atetosis puede hacer transición gradual al temblor parkinsoniano, el cual es visto como un conflicto más intenso de los mismos factores tónicos reflejos. Cuando éstos se desintegran la reacción laberíntica de enderezamiento es liberada y resulta la distonía hemipléjica. Esta reacción requiere fibras tálamopalidales intactas.

La interrupción quirúrgica de estas fibras disminuye la distonía y el conflicto de reacciones. La condición de distonía en flexión resulta de la pérdida de fibras tálamo-palidales y estrio palidales y es debida a reacciones exageradas de enderezamiento por contacto corporal. La aquinesia asociada es debida a la pérdida de factores corticales y reflejos en el movimiento.

RESUME

On n'a pas suffisament apprecié que la rigidité plastique de la paralysie agitante graduellement se fait plus résistente à l'allongement dans les groupes des muscles fléchisseurs, ce qui résulte dans une posi- mais la position terminale est de dystonie en flexion). Le changement est dû à la perte de la réaction d'étirement.

Cet état terminal de dystonie en flexion est celui qui est produit par la nécrose du pallidum dans l'empoisonnement avec du monoxyde de carbone. Dans le parkinsonisme familial, artériosclerotic et post encéphalitique arrivent les mêmes changements mais la position terminale est de dystonie hemiplegique (membres supérieurs en flexion et inférieurs en extension). Ce genre des dystonie est produit par de grandes lésions du putamen.

Une parte diffuse des systèmes de fibres du globus pallidum même, ou des systèmes strio pallidals produit du parkinsonisme. La perte des cellules nerveuses n'a pas d'importance jusqu'a des états tardifs. La lésion courante est la dégénération paravasculaire de Foix et Nicolesco.

Dans le parkinsonisme post encéphalitique il exist une perte diffuse de fibres corticostriées et striopallidals comme une partie d'un dommage celullaire plus étendu. La subtance noire apparait plus en relation avec la coordination bulbaire. La perte des fibres corticostriées conduit d'abord à l'athetose laquelle est un conflict de réponses toniques de prehension et de retraite.

Dans la maladie de Wilson l'athétose peut faire des transitions graduelles au tremblement parkinsonien lequel est considerée comme un conflict plus intense des mêmes facteurs toniques reflexes. Quand ceux-ci se desintégrent la réaction laberin-

tique de redressement est liberée, résultant la dystonie hemiplegique. Cette réaction doit avoir des fibres thalamo pallidales intactes. L'interruption chirurgicale de ces fibres diminue la dystonie et le conflict des réactions.

La dystonie en flexion résulte de la perte des fibres thalamo pallidales et striopallidales et elle est dû à des reactions exagerées de redressement, l'acinésie est due à la perte des facteurs cortical et reflex dans le mouvement.

ZUSAMMENFASSUNG

Es ist nicht genuegend betont worden, dass die plastische Starre der Paralysis agitans allmaehlich immer mehr resistet wird gegenueber der Streckung der Beugemuskelgruppen, was schliesslich zu einer terminalen fixierten Flexionshaltung fuehrt (Flexionsdystonie). Diese Veraenderung ist bedingt durch den Verlust der "Dehnungsreaktion". Dieser terminale Zustand der Flexionsdystonie ist verursacht durch die Nekrose des Globus Pallidus bei der Kohlenmonoxidvergiftung. Die gleichen Veraenderungen finden wir beim post-enzephalitischen, arteriosklerosen und familiaeren Parkinsonismus; jedoch ist die terminale Haltung die einer hemiplegischen Dystonie (die oberen Gliedmassen gebeugt und die unteren gestreckt). Diese Form der Dystonie ist durch grobe Laesionen des Putamen bedingt. Ein diffuser Verlust des Fibrillensystems des Globus pallidus selbst oder des strio-pallidaeren Systems produziert Parkinsonismus. Selbst in den letzten Phasen ist die Zerstoerung von Nervenzellen unbedeutend. Die gewoehnliche Laesion besteht in der paravasculaeren Degeneration von Foix und Nicolescu. Beim post-enzephalitischen Parkinson beobachtet man eine ausgedehnte Zerstoerung von cortico-striaeren und strio-pallidaeren Bahnen, als Teil einer ausgedehnten Zellserstoerung.

Die Substantia nigra scheint vor allem mit der bulbaeren Koordination zu tun zu haben. Der Verlust der cortico-striaeren Bahnen fuehrt zunaechst zur Athetose, die als ein Konflikt zwischen der tonischen Greif —und tonischen Vermeidungs— reflexen anzusehen ist. Bei der Wilsonschen Krankheit mag die Athetose ein allmaehlischer Uebergang zum parkinsonschen Tremor sein, welcher als ein intensiverer Konflikt der gleichen tonischen Reflexfaktoren angesehen werden kann. Sowie diese verschwinden, werden die labyrinthischen Stellreaktionen frei, wobei eine hemiplegische Dystonie entsteht. Diese Reaktion erfordert intakte thalamo-pallidaere Bahnen. Die Unterbrechung dieser Bahnen durch eine chrirurgische Intervention mindert die Dystonie und den Konflikt zwischen den Reaktionen. Die Flexionsdystonie entsteht durch die Zerstoerung sowohl der thalamo-pallidaeren als auch der strio-pallidaeren Bahnen und ist bedingt durch ueberaktive Stellreaktionen durch Koerperkontakt. Die beigeordnete Akinesie ist bedingt durch den Verlust der Rinden-und Reflexfaktoren bei der Bewegung.

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The Gamma System in Parkinsonism

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The sensory nature of mammalian muscle spindles was proved experimentally by Sherrington (1894) and, in a detailed histological study, Ruffini (1898) produced a series of beatifully clear and now well-known illustrations which show unambiguously the fine motor nerve fibres of these sense organs.

The fact that a sense organ received motor fibres, in addition to its sensory innervation, seems to have attracted little active interest until fifteen years ago, when Leksell (1945) made his study of the small motor fibre component of ventral roots. Since that time, a vast amount of experimental work has been performed to try to establish the rôle of these gamma motor fibres in movement, the nature of the gamma motoneurones, and their central connections. The gamma system is essentially a physiological conception; the name derives from the fact that the small motor fibres are responsible for the gamma wave in the ventral root potential, which is set up as a result of a single shock to an appropriate muscular nerve. It was thereby determined, in the cat, that these fibres conduct at 20-40 m/sec., which is much slower than the motor fibres (alpha fibres) supplying ordinary muscle fibres (60-100 m/secs.). This suggests that the gamma motoneurones are smaller cells than the alpha motoneurones, but apart from size there appear to be no clear histological differences in the motoneurones. Granit, Holmgren and Merton (1955) were able to show that midbrain stimulation can influence gamma motoneurone firing through two pathways and via the reticular formation. One of the pathways was fast and direct, the other relatively slow and very indirect. Anatomical correlates of these pathways, again, is rather sadly lacking, though Hassler (1960) guesses that the fast one is the nigro-reticulospinal tract.

Sense organs in muscles may seem a far cry from the pathetic patient with Parkinsonism, imprisoned by poverty of expression and movement, and shaken by spontaneous tremor, but it is the purpose of this paper to show how the gamma system and its outflow of small motor nerve fibres to muscle spindles produces a disorder of stretch reflexes — a basic postural mechanism from which movement is derived, accompanied and followed up. The disordered stretch reflexes manifest themselves as muscular rigidity which hampers not only passive displacement of limbs but also voluntary movement.

For James Parkinson (1817), the striking features of the disease that bears his name were the involuntary tremor and the lessened muscular power. This astute observer, in his "Essay on the Shaking Palsy", vividly described the natural history of the disease, beginning as a little trembling and weakness of limbs or head, then the characteristic posture with its static tremor, the disordered locomotion, the inarticulation and dribbling of saliva. Though his account was incomplete, there was little added to it for over half a century.

Winslow (1860), in his acconut of paralysis agitans (so called by Marshall Hall, 1841), remarks that "Mr. Parkinson has entered more fully than any other writer into a history of the precursory stage of

this disease, and to his treatise I am indebted for the subjoined and graphic resumé". He then proceeds to quote, verbatim, three-and-a-half pages of extracts from Parkinson's account.

Bastian (1886), in his book "Paralyses (cerebral, bulbar and spinal)", quite correctly has no mention of paralysis agitans, for it was not a paralysis in the true sense of the word and the site of the lesion had not been identified. Already, steps had been taken, however, to investigate the nature and the pathology of this strange disease.

Charcot (1889) illustrated one of his lectures with a tracing of the tremor of paralysis agitans, and though the tracing shown lacked a time scale, he stated in the text that the oscillations occurred, on an average, four or five times a second and were increased in amplitude by voluntary movement. Gowers (1893) presented a masterly, clinical analysis of Parkinsonism, illustrated the tremor, and compared and contrasted it with tremors recorded in patients with diseases such as multiple sclerosis, G.P.I., hemiplegia and hysteria. Parkinsonian tremor was seen to be extremely regular both in amplitude and rate, and, compared with other tremors, it was rather slow (5-7 a second). In all these features, it was the antithesis of the tremor in multiple sclerosis, and it was implied that the graphic method might be useful for diagnostic differentiation of tremulous conditions. In Gowers' brilliant account of paralysis agitans, stress was placed on the muscular rigidity of the patient, which was as characteristic, important and constant feature of the disease as the tremor. Moreover, he discusses the muscular rigidity and the muscular weakness together under a single heading —a prophetic gesture, years ahead of its time— linking disordered voluntary movement with disordered postural reflexes and the sure clue, we now believe, to much of the motor dysfunction of Parkinsonism. Rigidity was active muscular resistance to passive displacement of limbs or parts of limbs, and was usually greater in the flexor muscles, which imposed on the patient a characteristic posture of the body and limbs. It slowed the initiation of voluntary movements and limited their range, but it could be readily overcome by the examiner. The loss of muscular power was never absolute, and the striking feature was the change in the quality of the movement —slow and of small amplitude— largely due to the rigidity.

The clinical aspects of Parkinsanism were further clarified, in later years, by Wilson (1928, 1941), and an analysis of the disordered motor function was discussed by Walshe (1955) in an account which shows much insight into the problem. It appeared that Parkinsonism —a syndrome of motor dysfunctions— could arise as a result of encephalitis in relatively young patients, idiopathically in rather older patients, and rarely from other causes. Irrespective of the aetiology, however, the same pattern of disordered motor function could be made out, though there might be quantitative differences in the relative amounts of rigidity and tremor; the patient with postencephalitic Parkinsonism usually had more muscular rigidity and less tremor than the patient with idiopathic Parkinsonism.

This uniformity of the motor dysfunction would suggest, to some, an anatomical lesion of a specific part of the extrapyramidal system. For Hassler (1960) "The anatomical defect is destruction of nerve cells in the substantia nigra". Few Neuropathologists would be in complete agreement with this dogma, though Greenfield (1955 and 1959) found wider involvement of the melanin-bearing cells of the brain-stem and frequently atrophic changes in the globus pallidus, which, he postulated, was secondary to the lesions of the substantia nigra. Denny-Brown (1960) described the pathological changes in twenty-one cases examined in the Boston City Hospital. All cases showed some degree of pallor of the globus pallidus and the ansa lenticularis. In severe paralysis agitans, pallidal cells were shrunken and poorly stained, but in two out of nine cases there was neither cellular nor fibre lesion in the substantia nigra. In the arteriosclerotic cases of Parkinsonism, lesions of the putamen were more obvious than lesion of the pallidum. Only in the postencephalitic cases was there severe destruction of the substantia nigra in all cases, but there was also a diffuse pallor of the fibre

systems of the globus pallidus, a loss of fibres entering the external putamen from the external capsule (presumably originating in the parietal cortex) and fibres composing the external lamina of the globus pallidus (fibres which come from the internal capsule and probably from the motor areas of the cortex). Denny-Brown reminds us that destruction of the substantia nigra frequently occurs in the acute phase of encephalitis lethargica, yet without Parkinsonism at this stage. The interruption of cortical connections of the putamen and globus pallidus might well be intensely significant in the Parkinsonian syndrome.

The description and analysis of decerebrate rigidity by Sherrington (1898), and the demonstration of its reflex nature, gave a tremendous impetus for further study of muscular "tonus" and "hypertonus" both in animals and in man. The controversy and confusion of thought that ensued has been described elsewhere (Rushworth, 1960). Nevertheless, tremendous strides were made in the nineteen-twenties to the understanding of the basic mechanisms of the stretch reflex (Liddell and Sherrington, 1924), body posture and righting (Magnus, 1924), and the postural reflexes (Denny-Brown, 1929), which rendered the term "tonus" unnecessary and irrelevant.

In Britain, Walshe was one of the pioneers in the application of physiological thought and method to Clinical Neurology, and so far as this paper is concerned, his recordings from patients with paralysis agitans (1924), though long forgotten and ignored, are of fundamental importance and significance. The plasticity of Parkinsonian rigidity was described, and he clearly differentiated it from spasticity. Inspired by the paper of Liljestrand and Magnus (1919), who abolished the muscular rigidity of decerebrate rigidity in cats by intramuscular injections of procaine (novocaine) without effect on muscular power, Walshe injected procaine into the muscles of patients with paralysis agitans. Rather large amounts of 1 per cent procaine solution (10-20 ml.) were injected near the region of the motor point, for the idea was to narcotise afferent nerve fibres and, in this way, to interrupt the reflex arc maintaining rigidity. Foerster (1911) had previously done this directly in spastic children by section of dorsal roots, and Leriche (1914) in Parkinsonism. Shortly after the procaine injection, the muscular rigidity melted away —"...the change in these circumstances being as dramatic —and as transient— as the disappearance of myasthenic weakness under the influence of a dose of prostigmine"— (Walshe, 1955). The tremor and muscular power were unaffected, but both the speed and range (amplitude) of movement were *increased*. Though ataxia was very slight, Walshe (1924), believed the results were explained by a predilection of procaine in blocking afferent nerve (proprioceptive) fibres before efferent, and thus de-afferentating the injected muscles before paralysing them.

Over thirty years later, Matthews & Rushworth (1957*b*, 1958) showed that when dilute procaine was applied to a muscular nerve, both large afferent and large efferent fibres were somewhat resistant to the local anaesthetic and took a considerable time to block, but when they did so they were both anaesthetised equally and at the same time. The gamma motor nerve fibres, however, were particulary susceptible to procaine, and blocked rapidly after the application of procaine. These observations alone made it improbable that Walshe's explanation was completely correct, for large-fibred muscle afferents and efferents are equally resistant to procaine, and if muscular power were preserved after the injection of procaine (as Walshe showed it was) then the large afferent (proprioceptive) nerve fibres should also have been spared. The gamma motor nerve fibres specifically innervate the intrafusal fibres of the muscle spindle, and thereby adjust the sensitivity of the annulo-spiral ending to stretch-appropriately regulating proprioceptive impulses during muscular contraction. Walshe's results are compatible with the idea that intra-muscular injections of procaine act locally by blocking the gamma fibres of the injected muscle, so reducing the sensitivity to stretch of the muscle spindles. Large motor fibres would be unaffected at this stage (possibly not at all with this low procaine concentration and with its rapid

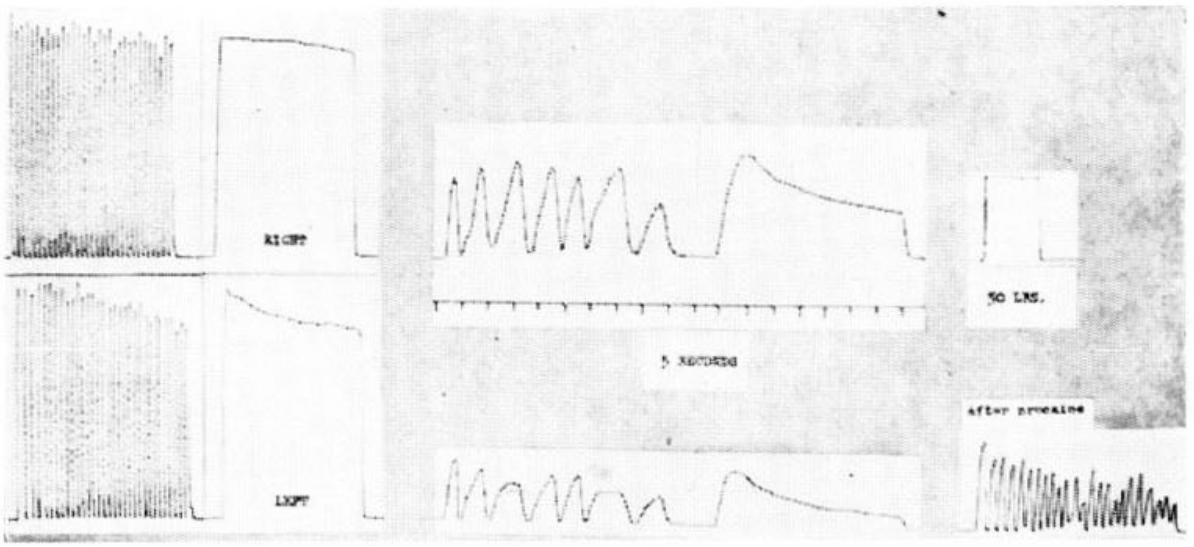
removal from muscle), and the same would be true for large sensory (proprioceptive) fibres so that neither paralysis nor gross ataxia would occur.

Matthews and Rushworth (1957*a*) further showed that dilute procaine abolished the hyperactive stretch reflexes of decerebrate rigidity in cats, long before there was any effect on the motor tetanus (at 100/sec.) initiated above the region of partial nerve block.

The time was then ripe for a study, by similar methods, of the increased stretch reflexes in human spasticity and rigidity, and Rushworth (1959, 1960) published his results on twenty-five patients with Parkinsonian rigidity, twenty with spasticity, and five with dystonia. Since then, a further group of twenty patients with Parkinsonism has been intensively investigated in an attempt to assess motor function before and after the operation of "thalamectomy" (Cooper & Bravo, 1958), and I am most grateful to my colleague, Mr. E. S. Watkins, for the opportunity of studying these patients.

Methods.

Apart from routine neurological examination and a ciné film of the patient's performance in a number of motor tests, simultaneous bilateral dynamometer records of finger grip are obtained both for rapidly repeated movements and for sustained action. Electromyograms are recorded from concentric needle electrodes within a flexor muscle and an extensor muscle in the more affected arm (usually the finger flexors and extensors), while finger tremor is recorded by a ceramic transducer (Rushworth & Willison, 1960), and a balloon pressure recorder over the wrist signals movement there, including stretching of the forearm muscles. (Some of these methods are detailed in Rushworth, 1960). Recordings by these methods give information about the power of the finger flexors, their speed of contraction and relaxation, and the ability to sustain contraction. Tremor is measured, and any change with voluntary movement; the effects of gentle movements and movements employing near maximal power are compared. Stretch reflexes in both flexors and extensors are recorded for a variety of speeds of stretching. Finally, it is of some interest to see the effect, on all these motor functions, of 10-20 ml. of 1 per cent procaine injected into either or both muscle groups.



a b c

Fig. 1. — a) Normal: Dynamometer records of simultaneous finger grip. Upper, right hand: lower, left hand. b) Postencephalitic Parkinsonism (N. R.). Before procaine. c) Same after procaine. Wide infiltration of flexors and extensors of left fingers with 15 ml. 1 per cent procaine 5 minutes previously.

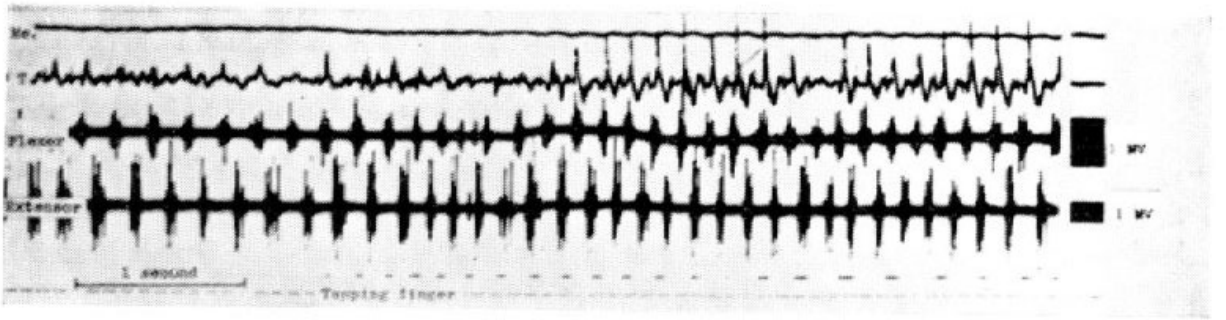


Fig. 2. — Idiopathic Parkinsonism (E. T.). Tapping the right forefinger on the transducer (T.) as fast as possible. Mechanogram (Me.) over wrist, electromyograms from flexor and extensor of first finger. Spontaneous tremor at firsrt, then at signal (dashes) tapping commences. Calibrations: 1 secons and 1 millivolt.

Voluntary Movement and Rigidity.

(a) Contraction and Relaxation.

Dynamometer records of simultaneous finger gripping show many of the features so characteristic of the disordered movement of Parkinsonism. The patient is asked to squeeze, with both hands, as fast and as hard as possible, and to repeat this action as quickly as possible. A record for a normal person is shown in Fig. 1(a). In a very rigid patient, such as one with postencephalitic Parkinsonism, a tracing was obtained [Fig. 1(b)], which showed the slow repetition rate (about 1 every 5 seconds compared with the normal of about 1 a second), the slow rise to the peak of the contraction of the finger flexors (about 2 seconds), and slow relaxation (over 1 second). The maximal power in this case was less than normal, and tremor showed itself in the contraction phase. When asked to maintain the grip, the power rather quickly declined [Fig. 1(c)] compared with the normal. Five minutes after injection of 15 ml. 1 per cent procaine into the proximal ends of both flexor and extensor muscles of the left fingers, the contraction and relaxation processes were very much speeded up, and the maximum repetition rate was then 3-4/5 seconds (i.e., an increase of about 4 times). The maximum power appeared to have increased slightly, possibly due to the increased range of movement that was then possi-

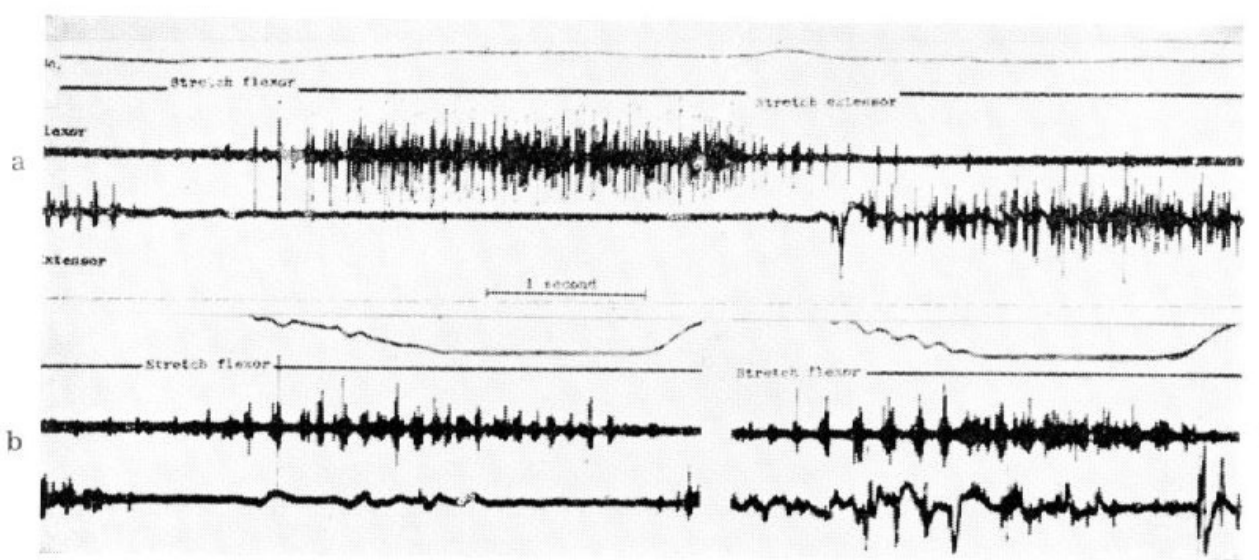


Fig. 3. — Idiopathic Parkinsonism (E. T.). Mechanogram (Me.) over wrist to signal muscle stretch. Electromyograms from flexors of fingers (upper record) and extensors of fingers (lower record). — Calibrations: 1 second and 1 millivolt as in Fig. 2. a) Effect of slow stretching. b) Effect of faster stretch. Cog-wheel rigidity appears. c) Effect of fast stretch.

ble. It was, however, much below the power of a normal hand grip.

Attempts at imitating piano playing often demonstrate defects in repetitive movement in even mild Parkinsonism. Individual finger tapping is a much less stringent test, but has the advantage of being more easily recordable. It is much more disordered in a patient with severe rigidity rather than tremor, and a patient with much tremor may be able to utilise it and speed up its alternation a little, in order to carry out the tapping (Fig. 2). It may then aproach that of normal people in rate (6/sec.), though the force of tapping is irregular and the range is limited. It is interesting to postulate whether this test could be done better by patients with a slightly faster tremor.

(b) The stretch reflex.

When the limbs of a patient with Parkinsonism are displaced by an examiner so as to stretch muscles, a characteristic mild resistance is encountered which is plastic, in that the resistance is easily overcome and the posture imposed may be maintained for a time. The resistance of muscles to passive displacement is felt, irrespective of the direction of movement and no matter whether flexor or extensor muscles are stretched, and its plastic qualities (lead-pipe rigidity) may be modulated by a series of jerks, particularly by fast stretches, so that cog-wheel rigidity results. The tendon reflexes are usually normal or, in very rigid patients, depressed. In patients with much tremor and little rigidity the tendon reflexes are sometimes very brisk.

The resistance to passive displacement is a tonic stretch reflex elicitated by stretching the muscle, and it is abolished by dorsal root section (Leriche, 1914; Pollock & Davis, 1930). In Parkinsonism it is pre-

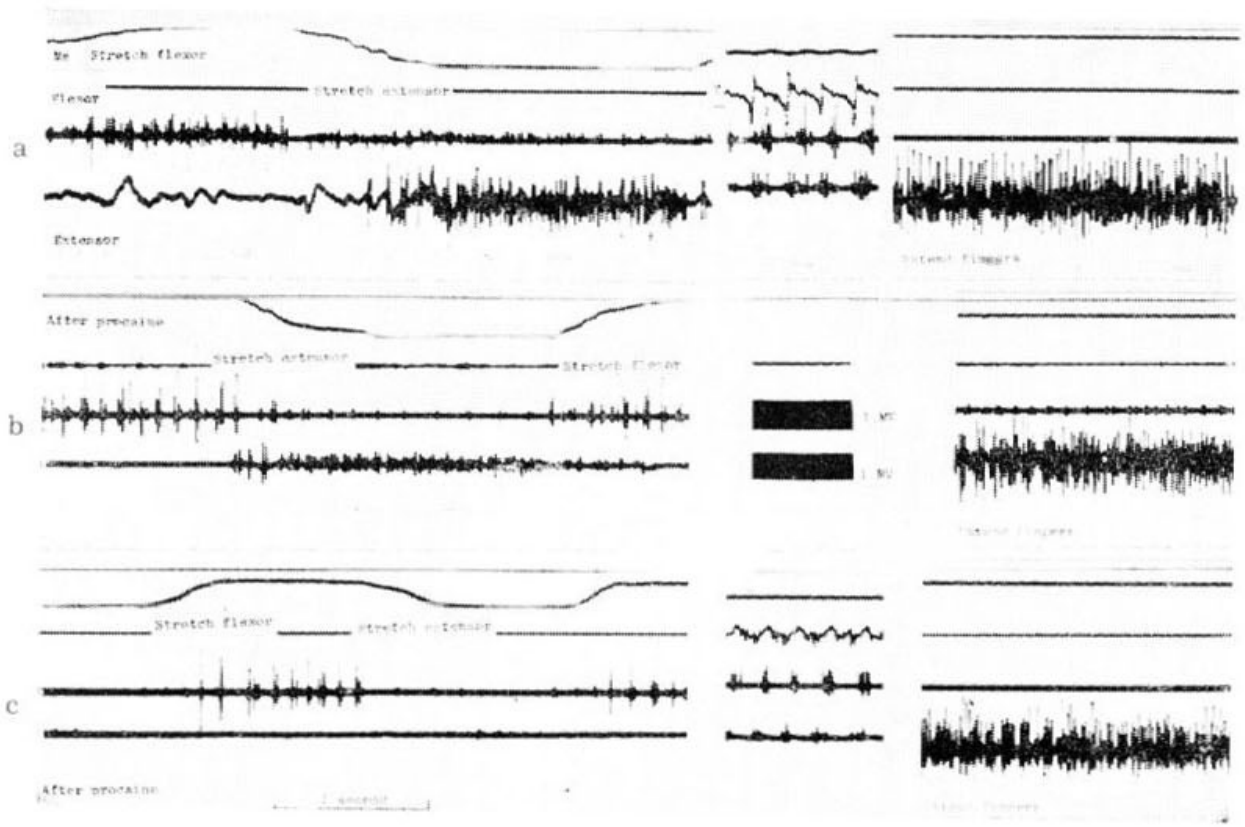
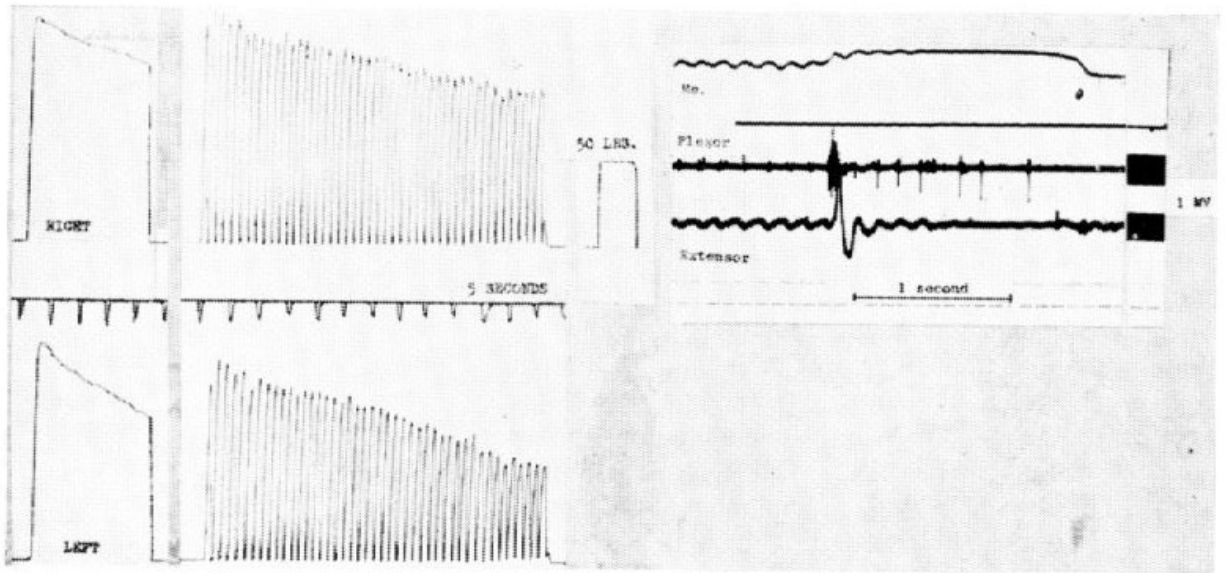


Fig. 4. — Idiopathic Parkinsonism (W. B.). Effect of procaine on rigidity. Mechanogram (Me.) over wrist to signal muscle stretch. Electromyograms from flexors of fingers (upper record) and extensors of fingers (lower record). — Calibrations: 1 second and 1 millivolt. a) Before procaine. Stretch responses, tremor and voluntary extension of finger. b) 3 minutes after procaine infiltration of extensors; stretch response of extensors considerably reduced, voluntary extension of fingers relatively unaffected. c) 5 minutes after procaine. Now no stretch response of extensors, though voluntary extension of the fingers is unaffected. The spontaneous tremor is a little reduced.



a b

Fig. 5. — Idiopathic Parkinsonism (R. R.). Much tremor, little rigidity. a) Dynamometer records of left and right finger gripping, both sustained and repeated movements are relatively normal though the latter is a little slow. — Calibration: 5 seconds and 50 lbs. b) Mechanogram (Me.) over wrist. Electromyograms from flexors (upper record) and extensors of left finger. Much spontaneous tremor and a brisk stretch response in flexors on stretching them.

sent in both flexor and extensor muscles (or other antagonistic pairs) of a limb, which is in marked contrast to spasticity, for here the tonic stretch reflex is characteristically exaggerated only in the antigravity muscle of an antagonistic pair. Parkinsonian rigidity is mild, plastic, and frequently of the cog-wheel variety, whereas the tonic stretch reflex of spasticity increases with increasing stretch until a certain maximum is reached and it is suddenly inhibited (by discharge of Golgi tendon organs) — the "lengthening reaction".

All the characteristic features of Parkinsonian rigidity may be seen in the electromyogram taken simultaneously from the extensors and flexors of the fingers (Fig. 3). Slow stretch resulted in bursts of motor units occurring almost simultaneously, so that as many as ten motor units might appear superimposed. Each single burst, however, was followed by a pause before another burst occurred, and this too was made up of many units and not necessarily the same ones that had already fired. The pause between each burst of motor units had no relation to the tremor rate, for it decreased considerably as stretch proceeded. [In Fig. 3(a) the bursts in the flexors began at 10/sec. and went on to about 25/sec.]. Even at maximum muscle stretch, grouping of discharges could be clearly seen. When stretch was relaxed the motor units did not necessarily stop firing, and there might be a brief and temporary increase of firing when stretch of the antagonist was commenced (Westphal's phenomenon, paradoxical contraction).

Each intense burst of motor units with increasing slow stretch is a brief tetanus and represents an exaggerated "tonic" stretch reflex which itself is sufficient to cause a steep increment of muscle tension and so briefly stimulate Golgi tendon organs. These, in turn, inhibit the active motoneurones and so a lengthening reaction occurs. This alternation, during slow passive stretch, of brief exaggerated stretch reflexes, immediately followed by brief lengthening reactions, will explain the plasticity of Parkinsonian rigidity. Its comparison with spasticity has been further described elsewhere (Rushworth, 1960).

For faster stretches [Fig. 3(b)], each quantal tonic stretch reflex may be so intense that the resulting small tetani are

more asynchronous and last longer than in slow stretches, and correspondingly longer lengthening reactions are evoked by the Golgi tendon organs. This permits each individual tetanus to be clearly felt during clinical examination, and the impression of a cog-wheel type of jerking is obtained. It is not the patient's tremor modulating the rigidity, for there are usually no alternating bursts of motor units in the antagonist, and the rate of "cog-wheeling" tends to increase with increasing stretch [Fig. 3(c)], and decrease with increasing initial speed.

The effect of procaine on this type of rigidity is very interesting. The response to stretch of the extensor muscle of the fingers of a patient with moderate rigidity [Fig. 4(a)] was similar to that already described. Within three minutes of wide infiltration of the proximal end of the extensor muscles with 15 ml. of 1 per cent procaine, the stretch response of the extensors was considerably reduced [Fig. 4(b)], though the voluntary innervation of the muscle was unaffected. By five minutes, the stretch response in the extensors was abolished [Fig. 4(c)] and voluntary innervation was unchanged, but the spontaneous tremor which occurred two minutes later was a little reduced both in amplitude and number of units firing.

The very clear differential action of procaine in abolishing the rigidity without, however, affecting voluntary innervation is most reasonably due to the blocking of the

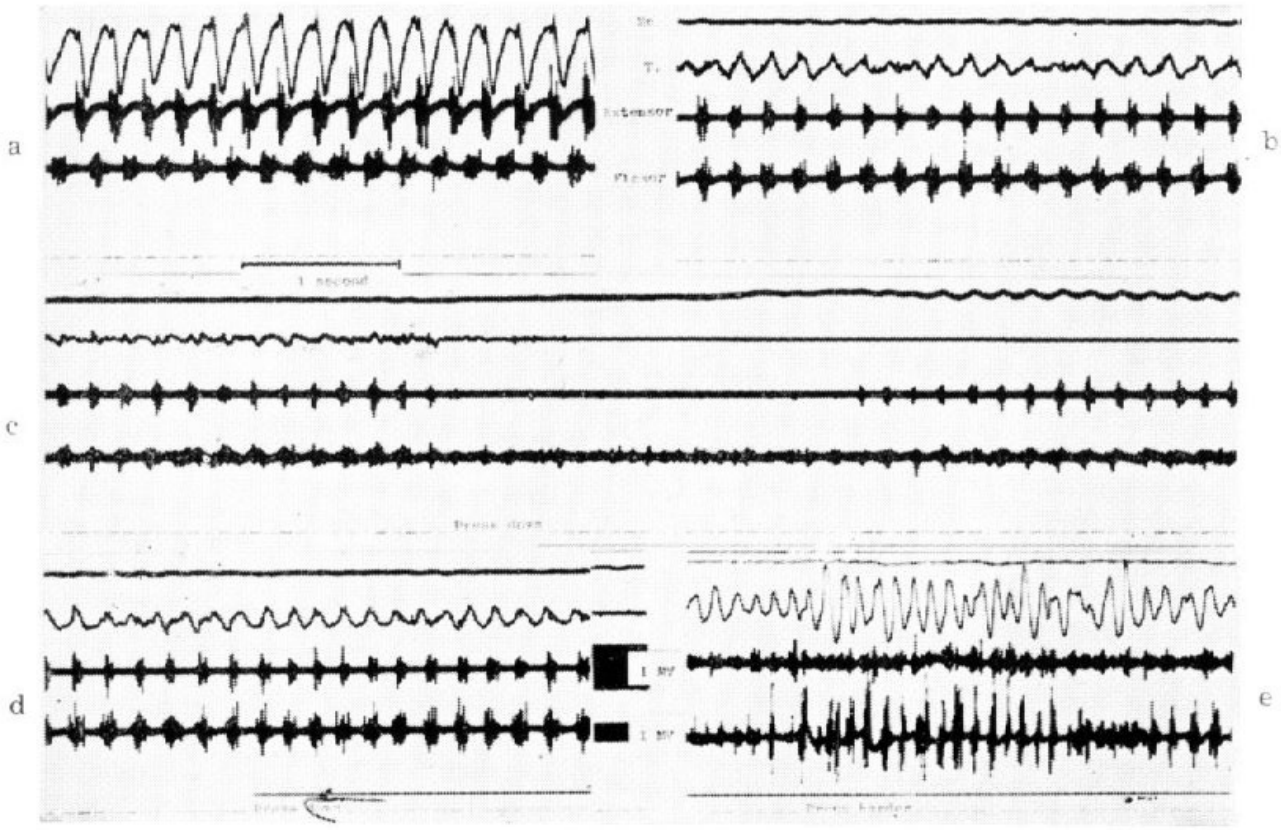


Fig. 6. — Idiopathic Parkinsonism (L. C.). Moderately rigid and much tremor. Mechanogram (Me.) over wrist, tremor is recorded from the right index finger by means of a ceramic transducer (T.), electromyograms from flexors (lower record) and extensors of right index finger (upper record). — Calibration: 1 second and 1 millivolt. — Transducer amplification constant. a) Spontaneous alternating tremor. Large amplitude. b) Spontaneous tremor in phase (simultaneous contraction of flexors and extensors), smaller amplitude. c) Voluntary activity abolishes the tremor, but it returns after a few seconds. d) Voluntary activity (pressing finger on transducer) has no effect on tremor. e) During prolonged recording of effects of pressing down, the tremor amplitude has decreased. At the signal the patient is told to push harder.

gamma motor nerve fibres to the muscle spindles. This follows from the experiments of Matthews and Rushworth (1957*a*, *b*, and 1958) for they showed that gamma fibres in muscular nerves are particularly susceptible to procaine, and that exaggerated stretch reflexes (tonic especially) are abolished simultaneously with them. Moreover, at this time, both large motor fibres and large sensory fibres (the simple elements of the stretch arc) were demonstrated to be intact.

As we have shown, the integrity of gamma motor fibres is essential for the maintenance of Parkinsonian rigidity, which itself consists of increased tonic stretch reflexes occurring in bursts and interrupted by brief lengthening reactions.

It would seem probable that the increased tonic stretch reflexes are due to an increased firing of the gamma system which thereby makes the muscle spindles oversensitive to stretch, and that the procaine cuts off the increased tonic gamma discharge.

This is almost certainly an oversimplification of the problem, which is complicated by the effects of afferent stimuli coming from antagonistic and synergistic muscles. One of these is the Westphal phenomenon which will be briefly discussed later.

Occasionally during the procainisation of biceps brachii muscle in very rigid patients, it has been observed that the previously small tendon jerk becomes exaggerated for a short time as the rigidity is decreasing. This has been frequently seen in severe spasticity (Rushworth, 1960) and has been thought to be due to occlusion of the tendon jerk (phasic stretch reflex) by the very high tonic stretch reflex.

In some cases of Parkinsonism, tremor and slowness of movement are the predominating symptoms, and rigidity may not be appreciated at all by the examiner. However, with prolonged examination employing various speeds of stretching, it is usually possible to demonstrate rigidity of a transient nature. Dynamometer recording in such a patient might be relatively normal [Fig. 5(a)] as might finger tapping, but

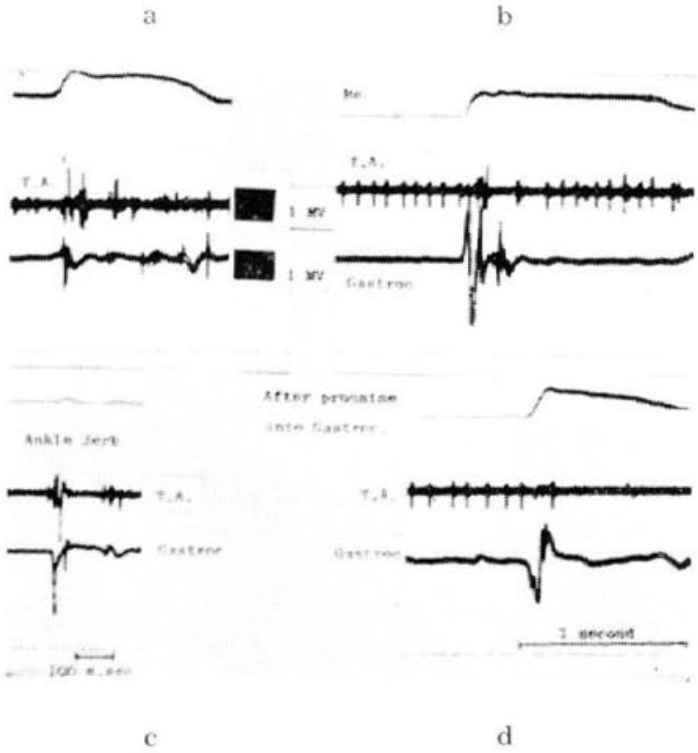


Fig. 7. — Idiopathic Parkinsonism (R. R.). Little rigidity. Mechanogram (Me.) over ankle signalling passive movement of foot. Electromyograms from tibialis anterior (T. A.) upper record, and gastrocnemius (Gastroc.) lower record. a) Sudden dorsiflexion of foot. Stretch response in gastrocnemius, the outburst in tibialis, slightly later, is the Westphal phenomenon. b) Slight voluntary tensing of tibialis anterior produces a single unit firing regularly. Sudden dorsiflexion of foot interrupts this with a burst representing the Westphal phenomenon followed by a silent period. Stretch response in Gastrocnemius partly obscured by movement artefact. c) The ankle jerk. A response follows in tibialis anterior about 40 m.secs. later. Time scale 100 m.secs. d) 5 minutes after wide procainisation of gastrocnemius. The Westphal phenomenon has disappeared, and the stretch response of gastrocnemius is reduced. Calibrations: 1 second and 1 millivolt.

five-finger piano-playing exercises could only be performed very slowly. The patient from whom records were taken was considered by the Clinicians to have no rigidity, but electromyograms from the forearm flexors and extensors clearly demonstrated a brisk but poorly maintained response to stretch in the flexors, and very little in the extensors [Fig. 5(b)].

(c) Tremor.

Parkinsonian tremor is characteristically a slow alternating tremor affecting flexors and extensors or other antagonistic groups of muscles. However, prolonged recording from the flexor and extensor muscles of the first finger, in a large number of patients, has shown that the tremor activity of these muscles is very variable. Sometimes tremor was present only in the flexor, sometimes in the extensor. Often it was exactly alternating [Fig. 6(a)] with a rate of about 5/second at rest, but at other times it might change phase so that tremor contradictions of flexor and extensor occurred almost simultaneously [Fig. 6(b)]. When this happened, the amplitude of tremor was less than when the contradictions were strictly alternating between the muscle groups.

The superimposition of voluntary movement usually, but not invariably, caused a temporary loss of tremor, but if the movement was continued, tremor returned at a slightly faster rate than at rest [Fig. 6(c), 6(d)]. In patients who have little rigidity, the tremor rate during voluntary activity (such as pressing the finger against the transducer) might increase from a resting rate of 5/second up to 10/second. During prolonged effort the tremor rate tended to fall both in amplitude and rate, but the request to push harder resulted in a striking increase again [Fig. 6(e)]. A great increase of tremor amplitude and a fall of tremor rate might occur if the patient is told to press only very gently.

It would appear that tremor amplitude is related to effort and particularly change of effort, and tremor rate is related to contraction power.

(d) Westphal Phenomenon. (Paradoxical contraction).

Occasionally in Parkinsonism, and other extrapyramidal disorders, sudden passive dorsiflextion of the foot results in an obvious contraction of the *shortened* muscle, tibialis anterior (Westphal, 1878, 1883). This reaction may also be seen in other muscle groups such as the forearm muscles. It has been studied by a number of workers, including Erlenmeyer (1880), Foix (1921), Goldflam (1922), Foix & Thévenard (1923) and Wilson (1928). The contraction of tibialis anterior was judged by the visible tightening of its tendon at the end of passive dorsiflexion, and this was also recorded by graphic methods. If the dorsiflexing pressure on the foot was suddenly relaxed, the attitude of dorsiflexion was often maintained for a time. The paradoxical contraction has been described as having two components, an initial phasic one and a later tonic contraction. The phenomenon is probably best seen in some of the moderately rigid patients with postencephalitic Parkinsonism, but a brisk phasic type of the Westphal reaction may be demonstrable in those cases of Parkinsonism which have relatively little rigidity. A record from such a case in shown is Fig. 7. When the foot was suddenly dorsiflexed passively, there was a burst of motor units in tibialis anterior, which, after a slight delay, followed the stretch reflex in gastrocnemius [Fig. 7(a)]. If the patient voluntarily tightened tibialis anterior, the Westphal phenomenon could be superimposed on this [Fig. 7(b)]. Tightening of the muscle, in this case, produced only a single unit response, and sudden dorsiflexion of the foot added a small burst of motor units followed by a silent period, lasting 1/10 second, before another little burst occurred, another silent period, and then resumption of the resting discharge rate.

If the ankle jerk is elicited in such a case, a paradoxical contraction may also be seen in tibialis anterior following the response in gastrocnemius by about 40 m. secs. [Fig. 7(c)].

Erlenmeyer (1880) believed that the Westphal phenomenon was due to the stretching of the antagonistic muscles, but this was strongly contested by Westphal (1883). Professor Denny-Brown and myself reinves-

rigated this point (Denny-Brown, 1960), and found that wide-spread infiltration of gastrocnemius muscle with dilute procaine abolished the paradoxical contraction of tibialis anterior without affecting the power of the injected muscles, though the ankle jerk was usually reduced or absent. This effect is shown in Fig. 7(d), recorded five minutes after infiltration of the gastrocnemius muscle with 20 ml. of 1 per cent procaine. Voluntary tightening of tibialis anterior produced a single unit response, and sudden passive dorsiflexion of the foot produced a small stretch reflex in gastrocnemius, but no Westphal phenomenon in tibialis anterior, though a short silent period occurred during the contraction of gastrocnemius.

It is postulated that the Westphal phenomenon is due to the stimulation, by stretch, of flowers-spray endings in the muscle spindles of the antagonistic muscles, for these excite flexor motoneurones in animals (Hunt, 1951). Calculations based on measurements of the delay of the paradoxical contraction of tibialis anterior following an ankle jerk, show that the afferent stretch impulses responsible for the Westphal phenomenon travel between 20 and 30 per cent of the velocity of those causing the ankle jerk. This would agree approximately with published measurements of the relative diameters and conduction velocities of fibres originating in the flower-spray endings of the muscle spindle (Group II fibres) and the fibres from the annulo-spiral endings of these organs (Group 1(a) fibres). (Lloyd & Chang, 1948).

The sensitivity to stretch of flower-spray endings as well as annulo-spiral endings may be increased by impulses transmitted along the gamma motor fibres. The abolition of the Westphal phenomenon of tibialis anterior by procaine infiltration of gastrocnemius can be explained by the blocking of the gamma motor fibres and of the Group II fibres (which are of similar diameter), thus reducing the stretch effects of the annulo-spiral endings (autogenous excitation) and abolishing those of the flower-spray endings (excitation of antagonist).

DISCUSSION

In a particularly dogmatic and contradictory account of the role of the gamma system in movement and its relationship to the extrapyramidal system, Hassler (Jung & Hassler, 1960) states that in Parkinsonism, gamma motoneurone excitability is absent or depressed. He goes on to say that "during many movements, gamma innervation precedes alpha innervation, the former having a kind of 'starter and function'; it is precisely this function, however, which is missing in Parkinsonism, in which the greatest difficulty is in starting of a movement".

Hassler's first statement derives from a single negative result of some of his own experiments (1956) in which he was unable to facilitate tendon reflexes in Parkinsonism by Jendrassik's manoeuvre. The work of Somner (1940), Hoffman (1951), and particulary Paillard (1955), made it likely that the enhancement of tendon reflexes by Jendrassik's manoeuvre was due to excitation of gamma motoneurones which then increassed the sensitivity of the annulo-spiral endings of the muscle spindles. Hassler, therefore, argues that because Jendressik's manoeuvre is ineffective in Parkisonism, the gamma motoneurones are inexcitable.

A much more plausible explanation of Hassler's findings is that the gamma motoneurones are in a constant state of excitation already, and that Jendrassik's manoeuvre cannot, therefore, add anything. Buller (1957) found this to be the case in hemiplegic spasticity, where, again, Jendrassik's manoeuvre was ineffective on the paretic side.

There is evidence, however, that disordered tonic stretch reflexes are the origin of Parkinsonian rigidity, and further discussion of tendon jerks (phasic stretch reflexes) is, therefore, rather irrelevant except to say that we have occasionally observed their local enhancement after procaine injection into the muscle (usually biceps), suggestive of occlusion by the tonic stretch reflex.

Numerous workers have described the precedence of the gamma motoneurone discharge over the alpha motoneurone dis-

charge in many reflexes. Hunt (1951); Kobayashi et al (1952); Eldred & Hagbarth (1954) demonstrated this for certain cutaneous reflexes; Granit, Job and Kaada (1952) for the pinna reflex; Eldred, Granit and Merton (1953) for the Magnus neck reflexes; and Rushworth & Denny-Brown (1959) for the grasp reflex. Unless the reflex has a secondary proprioceptive component (like the second component of the grasp reflex) it might still be elicited in the absence of the gamma system, for Eldred, Granit & Merton were able to elicit Magnus neck reflexes in de-afferentated limbs.

The function of the initial gamma motoneurone discharge, rather than alpha, is not a "starter function": it is to adjust the muscle spindle length so that the subsequent muscular contraction via the alpha fibres does not completely unload the spindles. If unloading of the spindles were to occur, then proprioceptive information would not be available during the contraction phase, and ataxia would result. This, indeed, can be shown by injection of dilute procaine into the muscles of normal subjects near the motor points in order to block the gamma motor fibres, when it is found that there is no change in the normal speed of contraction and relaxation, but the range of movement is irregular (Rushworth, unpublished observations).

The injection of dilute procaine into the muscles of a very rigid Parkinsonian patient regularly produces a dramatic effect in eliminating rigidity and in permitting much faster alternating movements to be carried out (Fig. 1). These facts are the very reverse of Hassler's postulate. From the electromyographic analysis of Parkinsonism and the procaine experiments presented in this paper, it is concluded that much of the disordered motor function of Parkinsonism is due to an overaction of the gamma system, particularly on the tonic stretch reflex. These views are shared by Schaltenbrand & Hufschmidt (1957), and the effects of procaine on rigidity have been confirmed independently by Numoto & Fukee (1959). Overaction of the gamma system produces oversensitisation of muscle spindles to stretch and this results in rigidity, which is plastic resistance of muscles to passive stretch, composed of alternate brief intense tonic stretch reflexes and lengthening reactions. The slowness of initiation, execution and relaxation of movement are due to a failure of the correct interaction of the postural reflexes and voluntary movement and, in particular, the inhibition of the rigidity of the antagonistic muscles.

There is, however, a much wider disorder of proprioceptive reactions in Parkinsonism than the simple stretch reflex arc and its gamma motor control, for the presence of the Westphal phenomenon in some cases of Parkinsonism shows up one of the disordered and exaggerated proprioceptive reflexes acting on antagonists. In an even wider field, Denny-Brown (1960) has analysed the disorder of motor function in Parkinsonism, and especially the presence and the relation of proprioceptive reactions to tonic grasping and avoiding mechanisms (Denny-Brown, 1956).

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SUMMARY

1) The evolution of ideas about the disorder of motor function in Parkinsonism, the recognition of rigidity as one of the principal signs with tremor, and the development of methods of studying the symptom-complex have been described.

2) A study has been made of simultaneous electromyograms taken from flexor and extensor muscles of the fingers during voluntary contractions, during bursts of spontaneous tremor, and during stretching. The rigidity is considered to consist of alternate, brief, intense, tonic stretch reflexes, followed by small lengthening reactions excited by stretch of Golgi tendon organs. This imparts the property of plasticity on the rigidity. It is postulated that the exaggerated tonic stretch reflexes are caused by hyperactivity of the gamma motor system, which oversensitises the muscle spindles to stretch.

3) Walshe's discovery (1924) that intramuscular procaine selectively abolished the muscular rigidity without affecting muscular power or the tremor, has been confirmed and reinvestigated by more modern methods and reinterpreted in the light of present knowledge about stretch reflexes and their supra-spinal control.

4) Intramuscular injections of dilute procaine in patients with much Parkinsonian rigidity and slowness of movement has resulted not only in abolition of rigidity but in a considerable speeding up of the initiation, execution, relaxation and repetition of movement involving the injected muscles. The range and sometimes the power of movement is slightly increased by the injection, and slight ataxia results.

5) Injections of intramuscular procaine near the motor point rapidly anaesthetise the gamma motor fibres of the muscle spindles (Matthews & Rushworth, 1957) at a time when the motor fibres of the muscle and large proprioceptive fibres are unaffected.

The abolition of Parkinsonian rigidity and the speeding up of Parkinsonian movement and its increase of range (and often power) by intramuscular procaine, have been explained as due to the preferential blocking of overactive gamma motor fibres leaving large motor and proprioceptive fibres intact.

6) The Westphal phenomenon (paradoxical contraction) is an example of a disordered proprioceptive reflex acting on an antagonist. It may be seen in tibialis anterior on suddenly stretching gastrocnemius-soleus. It is abolished by procainisation of gastrocnemius; latency studies show that it occurs about 40 m. secs. later than the ankle jerk. These suggest that the flower-spray endings of muscle spindles in gastrocnemius may be responsible for the reflex.

7) Spontaneous variations of tremor are described, and their changes in amplitude and rate with voluntary effort.

8) Tendon reflexes are usually not unduly brisk in Parkinsonism with much rigidity, but they may be very brisk when there is little rigidity. Occasionally during procainisation of very rigid muscles, the tendon jerk has become very brisk for a time. It is concluded that tendon reflexes in Parkinsonism may sometimes be occluded by high tonic stretch reflexes, as in spasticity (Rushworth, 1960). Hassler's (1956, 1960) finding that Jendrassik's manoeuvre does not enhance Parkinsonian tendon reflexes has been discussed and his conclusions from this, on the nature of Parkinsonian rigidity, are considered erroneous.

RESUMEN

1) Se describieron la evolución de las ideas acerca de las perturbaciones de las funciones motoras en el Parkinsonismo; la rigidez con temblor como signos principales y los métodos para estudiar el complejo sintomático.

2) Se realizaron estudios electromiográficos simultáneos en los músculos flexores y extensores de los dedos, durante contracciones voluntarias; mientras el temblor aparecía en forma espontánea y cuando se provocaba el estiramiento de los músculos. Se

considera que la rigidez es producida por la alternancia de breves e intensos reflejos tónicos de extensión, seguidos de pequeñas reacciones de estiramiento, consecuencia de la excitación de los órganos de Golgi, de los tendones con la extensión. Esto hace que la rigidez sea plástica. Se postula que la exageración de los reflejos tónicos de extensión es causada por la hiperactividad del sistema motor gamma por lo cual se sensibiliza el huso muscular en la extensión.

3) El descubrimiento de Walshe (1924) de que la procaina intramuscular produce la abolición de la rigidez muscular sin que se afecten la fuerza o el temblor, fue confirmado y vuelto a estudiar por los métodos modernos e interpretado a la luz de los conocimientos actuales acerca de los reflejos de estiramiento y su control supraespinal.

4) Las inyecciones intramusculares de procaina en pacientes con mucha rigidez parkinsoniana y lentitud en los movimientos, han dado resultado para abolir la rigidez, aumentar considerablemente la rapidez en la iniciación, ejecución y repetición de los movimientos producidos por los músculos inyectados.

Como consecuencia de la inyección, la amplitud y a veces la fuerza del movimiento se acrecientan un poco y de allí resulta una ligera ataxia.

5) Las inyecciones intramusculares de procaina próximas al punto motor, producen rápidamente la anestesia de las fibras motrices gamma de los husos musculares (Matthews y Rushworth 1957), aun cuando las fibras motoras del músculo y las fibras largas proprioceptivas no están afectadas.

6) El fenómeno de Westphal (contracción paradojal) es un ejemplo de un reflejo proprioceptivo desordenado que actúa sobre un antagonista. Puede ser observado en el tibialis anterior por la rápida extensión del soleo. Estudiando la latencia se demuestra que llega 40 milisegundos más tarde que el reflejo aquiliano. Esto sugiere que las terminaciones de los husos musculares en el gastrocnemio pueden ser responsables por el reflejo.

7) Se describen las variaciones espontáneas del temblor y sus cambios de amplitud y frecuencia con el esfuerzo muscular.

8) Habitualmente, los reflejos tendinosos no son muy vivos en el Parkinsonismo con mucha rigidez; pero pueden ser muy vivos cuando hay poca rigidez.

A veces durante la procainización de músculos muy rígidos, los reflejos tendinosos se hacen transitoriamente vivos. Se puede concluir que en el Parkinson los reflejos tendinosos pueden a veces ser detenidos por fuertes reflejos tónicos de estiramiento como en la espasticidad (Rushworth 1960). Se discutió la observación de Hassler (1956-1960) de que la maniobra de Jendrassik no aumenta los reflejos tendinosos en el Parkinsonismo y se considera errónea su conclusión acerca de la naturaleza de la rigidez Parkinsoniana.

RESUME

1) On a décrit l'evolution des idées au sujet du désordre de la fonction motrice dans le parkinsonism, la constatation de la rigidité comme une des principaux signes avec tremblement et le développement des méthodes pour étudier le complexe symptômatique.

2) On a fait des études electromyiographiques prises simultánement des muscles fléchisseurs et extenseurs des doigts pendant des contractions volontaires, pendant les déclanchements de tremblement spontanés et pendant l'étirement.

On considére que la rigidité et produite par des réflexes d'étirage toniques intenses brefs, alternés; suivis par des petites réactions d'allongement excitées par l'étirement dans le organes de Golgi des tendons. Cela fait que la rigidité soit plastique. On croit que les réflexes d'étirement toniques exagérés sont par l'hiperactivité du système moteur gamma lequel sensibilise les fuseaux musculaires à l'étirement.

3) La décourete de Walshe (1924) que la procaíne intramusculaire produit l'abolition de la rigidité musculaire sans affecter la force musculaire ou le tremblement, a été confirmée et recherché par des méthodes plus modernes et interpretés de nouveau à la lumière des connaissances présentes au

sujet des reflexes d'étirement et leur control supraspinal.

4) Les injections intramusculaires de procaine diluée dans des malades avec beaucoup rigiditée Parkinsonienne et lenteur dans des mouvements, résultèrent non seulement dans l'abolissement de la rigidité mais aussi dans une considérable accélération dans l'initiation, exécution, relachement et répétition des mouvements dans lesquels sont inserés les muscles injectés.

L'ampleur et quelquefois la force du mouvement est un peu augmentée à cause de l'injection et il en résulte une legère ataxie.

5) Les injections de procaine intramusculaires près du point moteur, anesthésient rapidement les fibres motrices gamma des fuseaux musculaires (Matthews et Rushworth 1957) même quand ne sont pas affectées les fibres motrices du muscle et les larges fibres proprioceptives.

6) Le phénomène de Westphal (contraction paradoxale) est un exemple d'un réflexe proprioceptive désordenné exerçant sur un antagoniste. On peut le voir dans le tibial antérieur étirant brusquement le soleogastrocnemius. Etudes de latency démontrent qu'il arrive autour de 40 m. secs. plus tard que le réflex achiliene. Ceci suggère que les terminaisons dans les fuseaux musculaires dans le grastrocnemius peuvent être responsable par le réflexe.

7) On décrit des variations spontanées du tremblement et son changement en amplitude et fréquence avec l'effort volontaire.

8) Les réflexes tendineux habituellement ne sont pas très vifs dans le Parkinsonism avec beacoup de rigidité mais ils peuvent être très vifs quand il y a peu de rigidité.

Occasionnellement pendant la procaínisation des muscles très rigides, le réflexe tendineux a été pour un temps très vif. On peur conclure que les réflexes tendineux dans le Parkinsonism peuvent quelquefois être arrêtés par de forts réflexes toniques d'etirage comme dans l'spasticité (Rushworth 1960). On a discuté l'observation de Hassler (1956-1960) que la manoeuvre de Jendressik n'augmente pas le réflexes tendineux du Parkinsonism et on considère érronée sa conclusion au sujet de la nature de la rigidité Parkinsonienne.

ZUSAMMENFASSUNG

1) Die Entwicklunk der Ideen ueber die motorische Funktionsstoerung beim Parkinson, die Erkennung der Rigiditaet mit Zittern als eines der wichtigsten Symptome und die Entwicklung der Methoden der Untersuchung dieses Symptomkomplexes werden beschrieben.

2) Es wurden Elektromyogramme gemacht gleichzeitig von den Beuge und Streckmuskeln der Finger waehrend freiwilligen Kontraktionen, waehrend Episoden von spontanem Zittern und waehrend des Streckens. Man betrachtet die Rigiditaet als alternierende, kurze, intensive und tonische Streckreflexe, gefolgt von kurzen Reaktionen der Verlaengerung, erregt durch Streckung der Golgi'schen Sehnenorgane. Dies gibt die Eigenschaft der Plastizitaet und Rigiditaet.Man glaubt, dass übertriebenen tonischen Streckreflexe verursacht sind durch Hyperaktivitaet des "Gamma motorischen System", welches die Muskelbuendel zur Streckung uebersensibilisiert.

3) Die Entdeckung von Walshe (1924), dass die intramuskulaere Verabreichung von Procain die Muskelrigiditaet selektiv unterdrueckt ohne die Muskelkraft oder das Zittern zu beeinflussen, konnte bestaetigt werden durch moderne Untersuchungsmethoden und wurde interpretiert im Licht unserer modernen Kenntnisse ueber die Streckreflexe und deren supraspinale Kontrolle.

4) Intramuskulaere Injektionen von verduenntem Procain bei Patienten mit starker Parkinson-Rigiditaet und langsamen Bewegungen verursachen nicht nur Verschwinden der Rigiditaet, sondern auch eine betraechtliche Beschleunigung des Beginns, der Ausfuehrung, der Relaxation und des Wiederholens der Bewegungen der injizierten Muskeln. Das Bewegungsausmass und manchmal auch die Karft sind leicht vermehrt durch die Injektion und es stellt sich eine leichte Ataxie ein.

5) Die Injektion von intramuskulaerem

Procain nahe dem motorischen Punkt anaesthesiert schnell die Gamma motorischen Fasern der Muskelbuendel (Mattews und Rushworth, 1957), waehrend die motorischen Muskelfasern und die langen propriozeptiven Fasern nicht beeinflusst werden.

Das Verschwinden der Parkinson-Rigiditaet und die Verbesserung der Bewegungen und deren Ausmass (und oft auch der Kraft) durch intramuskulaeres Procain wurden erklaert durch Blockierung der ueberaktiven Gamma motorischen Fasern, waehrend die langen motorischen und die propiozeptiven Fasern intakt bleiben.

6) Das Westphal Phenomen (paradoxe Kontraktion) ist ein Beispiel eines gestoerten propiozeptiven Reflexes, der als Antagonist wirkt. Es kann beobachtet werden beim M. tibialis anterior bei ploetzlicher Streckung des gastrocnemius-soleus. Es wird verhindert durch Procainisation des gastrocnemius; Latenzstudien zeigen, dass dies circa 40 m. sec. spaeter als der Achillesreflex auftritt. Das spricht dafuer, dass blumenbuquet-aehnlichen Enden der Muskelbuendel des gastrocnemius fuer den Reflex verantwortlich sein koennen.

7) Es werden spontane Variationen des Zitterns beschrieben und ihr Wechsel in Amplitude und Geschwindigkeit bei freiwilligen Anstrengungen.

8) Die Sehnenreflexe sind meist nicht besonders bruesk bei Parkinson mit starker Rigiditaet, aber sie sind sehr bruesk, wenn wenig Rigiditaet vorhanden ist. Waehrend der Procainisation von sehr rigiden Muskeln werden die Sehnenreflexe manchmal sehr bruesk waehrend einer gewissen Zeit. Daraus wird der Schluss gezogen, dass die Sehnenreflexe beim Parkinson manchmal verhindert sein koennen durch stark tonische Streckreflexe, wie z. B. bei Spastizitaet (Rushworth, 1960). Hasslers Entdeckung, dass das Manoever von Jendrassik die Sehnenreflexe bei Parkinson nicht verstaerkt, wird diskutiert und die Folgerungen daraus betreffend der Natur der Parkinson Rigiditaet werden als irrtuemlich betrachtet.

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The Pathology of Parkinson's Syndrome: a Critical Review

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James Parkinson in 1817 described 6 patients with "shaking palsy", two "noticed casually in the street" and a third "only seen at a distance". We honor this excellent observer with the eponyms Parkinson's syndrome and parkinsonism, but may note some deficiencies of his observations, at least one defect being related to the practice of medicine at a time when the physician did not often place his hands upon the extremities of the patient. Parkinson nowhere describes rigidity or the cogwheel phenomenon. He notes "the propensity to bend the trunk forward", today considered a consequence of rigidity, but described by him as "referable to such a diminution in the nervous power in the extensor muscles... as prevents them from performing the offices of maintaining the head and body in an erect position". Masked face and decreased eyeblink were not described. That "the tremolous motion of the limbs occur during sleep" is not usually thought to be correct today. Parkinson's confidence that "anatomical examination (is) the only sure foundation for pathological knowledge" may not be echoed by reviewers of more than a hundred years of anatomical reports on his disorder, nor by those aware of the difficulties of anatomical examination by existing techniques.

Parkinson conceived by what he deprecated as mere conjecture that the cause was a diseased state of the upper part of the spinal cord in the cervical region "and extending, as the disease proceeds, to the medulla oblongata". The view thereafter came to wide acceptance that the malady was a psychoneurosis. This opinion was supported by evidence of worsening of symptoms with emotional upsets, relief when mental tensions were relaxed, and by the absence of lesions discoverable by available methods. Erb (1909) believed "beyond doubt that psychical and somatic traumata may produce the disease". Reports of anatomic changes were published in the late 19th century, but in 1903, Osler stated that the lesions were not constant, and attributed the disease to "premature senility of certain regions of the brain", although this concept was vigorously denied by others.

Anatomical workers in the 19th century concentrated their efforts on the spinal cord and medulla, but emphasis at the beginning of the 20th century shifted to the corpus striatum after the work of Jelgersma (1908), Lewy (1912, 1914, 1923) and the Vogts (1920). Lewy (1912) described intra-cytoplasmic inclusion in neurons, and also (1914) alterations of neurofibrils. The substantia nigra became of interest in this disease as a result of reports by Blocq and Marinesco (1894) and later the epidemic of lethargic encephalitis with cases reported in the thesis of Trétiakoff (1919). This epidemic during the first World War was followed by many cases clearly designated as postencephalitic parkinsonism, but subsequently the role of encephalitis became less certain; it is generally assumed that cases of parkinsonism occurring years after

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the last known cases of lethargic encephalitis around 1926 have no relation to that epidemic. This general concurrence has not been without dissenters who have proposed that all cases are secondary to either recognized or unobserved encephalitis. The latter condition is more readily diagnosed than proved.

PATHOGENESIS

Most modern textbooks list the following as etiologic agents: arteriosclerosis, encephalitis lethargica and rarely other encephalitides, syphilis, trauma, carbon monoxide and carbon disulfide intoxication, manganese and other metallic poisons, rarely cerebral tumors, and most recently some of the tranquilizing drugs. Doubt may be raised as to whether some of these agents produce a progressive disorder, but even if symptoms are mimicked, the question of a cause and effect relation is not settled. Temporal sequences do not establish such a relation, as when parkinsonism follows cranial trauma. It may be and has been contended that trauma merely unmasks an underlying condition.

The role of some presumably causative agents has been denied because the disorder rarely occurs after the inciting factor, but this rarity is not decisive proof of a lack of relationship. For example, post-vaccinal encephalitis may occur only once in a million inoculations. Our present state is that we do not know which agents cause paralysis agitans; hence can neither affirm nor deny on scientific grounds, but seemingly decisive papers have been written on the basis of firm conviction. The usual classification of the disorder is into idiopathic, arteriosclerotic and postencephalitic types. Because of limitation of space, we shall mainly discuss these three forms and reduce them to two.

The role of arteriosclerosis as a pathogenetic agent in paralysis agitans is often accepted, but even those who question the evidence (viz Denny-Brown, 1954 who states "none of these factors satisfactorily explain the pathogenesis of parkinsonism") still succumb to the weight of custom and describe arteriosclerotic parkinsonism as a separate entity.

In considering the relation of arteriosclerosis to parkinsonism, it should first be recalled that concurrent disorders are not necessarily related etiologically. Gray hair and wrinkled skin are found in old people, but so far as is known, gray hair does not cause wrinkles, nor do wrinkles cause a loss of hair color. Arteriosclerosis and parkinsonism are frequent in persons beyond 40 years of age and may even occur simultaneously, but paralysis agitans also may be found without anatomic evidence of vascular disease, and conversely, severe vascular disease may be present in the corpus striatum and elsewhere without symptoms of shaking palsy. Arteriosclerosis of the cerebrum in an older person is therefore neither a necessary nor a sufficient condition for the development of parkinsonism. It cannot be denied that a particular pattern of vascular disease and neural alteration may be a possible mechanism, but as will be noted in the discussion of the anatomic lesions, such a pattern has not been demonstrated.

If arteriosclerosis were an effective cause of Parkinson's disease, it might be expected that diabetic patients, being subject to a higher incidence of arteriosclerosis than the general population, would have a higher incidence of Parkinson's disease. Kurland (1958) gives a prevalence rate of Parkinson's disease in Rochester, Minnesota, as 187 per 100,000. Patrick and Levy (1922) found 1 diabetic in a series of 146 parkinsonian patients. Joslin (1959) reported 50 cases of paralysis agitans in 3174 diabetics with nervous system involvement seen during an 11 year period. Unfortunately, the total number of diabetics studied is not given. The number of "cerebrovascular accidents" in the same group was 684, a figure a different order of magnitude and more probably related to the incidence of arteriosclerosis. More information is needed on the coincidence of these disorders.

The pathologist making the diagnosis of arteriosclerotic parkinsonism often uses the clinical history as supporting evidence. Keschner and Sloane (1931) state "in many of these cases, unless the pathologist has

some information as to the onset and clinical history of the case in addition to the anatomic observations, a positive pathologic diagnosis may be impossible". The pathologist therefore calls upon clinical evidence to support his diagnosis, but here too he finds a shaky floor beneath him.

The usual clinical methods for distinguishing the idiopathic and arteriosclerotic types were tabulated by Doshay (1954), although in 1960 he stated "for clinical purposes, all arteriosclerotic cases can be regarded as idiopathic or true Parkinson cases". The age of onset was given as 40 to 55 years for idiopathic and 55 to 70 for arteriosclerotic types. It is difficult to accept such a sharp line, and indeed, many of our own cases of parkinsonism beginning after 55 have been free from vascular disease. A different age of onset is not evidence of a different etiologic agent. The virus of poliomyelitis, for example, may affect young or old at different times and in different epidemics, and a change in age of incidence in the United Sstates has recently been noted (Statistical Bulletin, 1956); yet the same etiologic agent has been found.

The presence of hypertension or of arteriosclerosis elsewhere in the body cannot be used to prove the presence of arteriosclerosis in the brain, nor do these findings provide evidence of the etiologic role of vascular disease in causing parkinsonism. Doshay (1954) further differentiates idiopathic from arteriosclerotic parkinsonism by the mode of onset, being sudden in the former and evanescent in the latter. Most modern authors are more in agreement with James Parkinson that the onset of paralysis agitans is "so slight and nearly imperceptible... that it rarely happens, that the patient can form any recollection of the precise period of its commencement".

Although it is often stated, as by Doshay (1954), that rigidity is more prominent in the arteriosclerotic form, and tremor in the idiopathic, numerous instances are reported and have been seen by us in which rigidity dominated the clinical picture but necropsy disclosed absence of vascular disease, or in which tremor occurred with concomitant arteriosclerosis. Both tremor and rigidity are present in most cases of parkinsonism; the dominance of one or the other is caused by unknown factors, and should not be used as evidence of the etiologic agent.

Keschner and Sloane (1931) while calling on the clinician for help agree that the various clinical criteria are of "only secondary... importance", but "the association of a parkinsonian syndrome with symptoms and signs referable to focal cerebral or cerebellar disease... may be said to be the pathognomonic feature of arteriosclerotic parkinsonism". A more accurate statement is that the two disorders may be concurrent, but not that they are related as cause and effect. It would indeed be equally logical to decide that parkinsonism caused the focal cerebral disease. From these considerations, we conclude that clinical grounds are inadequate for the separation, anatomic methods are unsuitable, and the combined technics suffer from the inadequacies of both. Evidence has not been produced to show how arteriosclerosis may cause parkinsonism; the term arteriosclerotic parkinsonism probably should not be used until such evidence is available.

Postencephalitic parkinsonism is related mainly to the epidemic of encephalitis of von Economo, occurring approximately from 1914 to 1926. Few other encephalitides have been reported as causing Parkinsonism. It is assumed that the epidemic of the first World War was viral in origin, but direct proof is lacking. Onset of parkinsonism has been described as occurring many years after the bout of encephalitis, but it is difficult to accept this relation as cause and effect. Even if a virus were present, it would be unique in causing a progressive disorder rather than an acute illness with subsequent recovery or death. It was much easier to diagnose postencephalitic parkinsonism when cases occurred soon after epidemic, but as the years have passed, less certainty exists. The clinical syndrome is defined as a febrile and soporific illness followed by parkinsonian symptoms occurring usually in a young person and accompanied by a high incidence of pupillary and oculomotor abnormalities, including oculogyric crises, more rigidity than tremor, and the presence of autonomic symptoms such as sialorrhea and oily skin.

Numerous problems arise on further study. Patients indistinguishable from the previous description often lack a history of encephalitis; these cases were called "indeterminate" by Dimsdale (1946). To diagnose these patients as postencephalitic is to go beyond available evidence. Such a diagnosis does not answer the problem of pathogenesis: why do most people with lethargic encephalitis *not* get parkinsonism? Oculomotor crises are rare even in the encephalitic type. The ocular abnormalities are a reflection of encephalitis, but do not indicate that the inflammation caused parkinsonism. The so-called autonomic symptoms may occur in any other form of the disorder. Finally, Benda and Cobb (1942) have described large numbers of cases clinically called idiopathic which were cases of inflammatory brain disease on microscopic examination. Anatomically, one may accept the findings of inflammation and relate them to some form of encephalitis. But "burnt-out" encephalitis in which all inflammation has disappeared requires assumptions not readily proved. We conclude that a type of parkinsonism called postencephalitic exists, but that, except in the cases occurring around the time of World War I, it is difficult to prove, and that except for a few survivors, this form of the disease has disappeared.

PATHOLOGY

The problems in determining anatomic changes in idiopathic parkinsonism are shown in the confusing and contradictory reports. The lesion was said to be predominantly in the globus pallidus by Lewy in 1912, and confirmed by the Vogts (1920) and others. But Hassler (1937) and Klaue (1940) found no lesions in the pallidum, only in the substancia nigra, and were unable to distinguish idiopathic from postencephalitic disease anatomically. Lewy (1914) described severe loss of large nerve cells in the putamen, Keschner and Sloane (1931) mild loss, Bielschowsky (1920) loss of both large and small neurons, and Klaue (1940) no loss of any of these cells. Lesions in the cerebral cortex, the thalamus, the brain stem and spinal cord have also been affirmed and denied (Heath, 1947). Greenfield (1955) among others states that the substantia nigra is invariably altered, but Mathieu and Bertrand (1929) described patients with parkinsonism without any lesions in the substantia nigra. The peculiar intracytoplasmic inclusions described by Lewy have been found in all idiopathic cases by Beheim-Schwarzbach (1952), in 85 % by Lipkin (1959), and Alvord (1958) found them in only 1 case in 5 (20 %). Both Lipkin (1959) and Greenfield and Bosanquet (1953) found them less often in postencephalitic cases, but Beheim-Schwarzbach reported none. The incidence of the inclusions in controls is even more variable: Ciarla (1915) found Lewy bodies in all controls over 50 years of age, but Klaue (1940) found none. The inclusions also have been described in neurologic disorders without parkinsonism (Okazaki, Lipkin and Aronson, 1961). Similar difficulties are encountered in studies of the Alzheimer neurofibrillary change, extent of demyelination, and degree of reactive gliosis.

A summarizing statement might be: the substantia nigra is most often, but not always, affected in parkinsonism, its neurons diseased or decreased in number. The pallidum is next most frequently affected, and other parts of the central nervous systems may or may not be involved. The changes are not specific. A lipid pigment is often found in affected cells, and the cell bodies undergo slow dissolution. Myelin sheaths may be normal, irregularly decreased in number, or decreased ("pale") in specific tracts. Blood vessels and the supporting stroma may or may not be affected. Reactive gliosis may be nil, minimal or moderate, or severe. Intracytoplasmic inclusions occur in melanin-containing cells more often in idiopathic than in postencephalitic cases; but they are found in other neurologic disorders and in older patients without neurologie disease. Alzheimer neurofibrillary changes occur more often in postencephalitic than idiopathic cases, but are found also in older persons and in other neurologic disorders. Many of the described changes therefore may be encountered in old age without neurologic disease.

This summary must leave the reader

uneasy. The confusing mass of information is the result of what Parkinson called "the only sure foundation for pathological knowledge". Wherein arises the difficulty? Contemplation reveals possibilities of trouble arising from the clinical material studied, the technic of handling material from necropsies, and the criteria of anatomic diagnosis. We have dealt with the difficulties of determining the etiologic agent on the basis of clinical observation. There is little doubt that subdivisión of Parkinson's disease into 3 clinical types has often been whimsical and based on inadequate evidence. Little wonder then about the confusion when a pathologist reports findings in a case of idiopathic parkinsonism which another clinician would have called arteriosclerotic. But the technics of the pathologist are equally suspect.

Pathology is mostly an impressionistic art. The problem is not unusual in medicine. Therapists frequently find different results in "double blind" tests than when they have full knowledge of the individual therapy. Radiologists interpreting roentgenograms of the chest may differ among each other, and a single reader may disagree with himself two weeks later (Garland, et al., 1952). The technical difficulties confronting an interpreter of anatomic findings begin with the obtaining of human material at various times after death. Alteration of neurons, especially of Nissl substance, begins at the moment of death. The time of removal of the brain is a variable factor; the length of immersion in the fixative is another. The basal ganglions are farthest away from the fixative in uninjected brains. Changes in weight occur during the process of fixation. Embedding the fixed material in celloidin causes shrinkage, but to a lesser degree than the more common paraffin embedding. Shrinkage is related predominantly to extraction of water, and can result in apparent changes in numbers of neurons in a unit volume. Cutting at different thicknesses may be a more important factor for the illusion of cell loss. If a block of tissue supposedly cut at 8 microns is actually cut at 6, the thinkness is reduced by 25%; thin sections will contain fewer cells than thick sections. Changes in thickness may depend on variations in setting the microtome, but may occur at the same setting with continued use of a machine. Furthemore, staining is better performed and studied in large cells, tracts and fibers than in small ones. Important changes in small structures may occur without being detected.

Observer bias and observer error are well known phenomena. The pathologist approaches a slide with a concept of "normal" contained within his mind. He seldom uses controls done at the same time and under the same conditions as the pathologic material. Such controls ideally would include persons of similar age, sex and background without neurologic disease, but also with other neurologic disease. If the pathologist believes in the capacity of the clinician to distinguish idiopathic from arteriosclerotic types, he will perhaps too readily find evidence of vascular disease. If he accepts an encephalitic origin, but does not detect inflammation, he may assume the process has resorbed. Bias also may be exhibited by selection of a limited number of regions for study. An observer believing the disease is related to the basal ganglions may not take any or as many blocks from the spinal cord, cortex or thalamus. The observer may begin his observations with the notion that neurons in certain regions (the basal ganglions) are the source of the disease, and spend little time reviewing neurons or other structures elsewhere. Knowing vascular disease should he present, he may find it. The lack of specific changes also allows bias because findings may be described as indicating disease, but technics are not available to prove the diagnosis, or reveal that an error in interpretation has been made.

Criteria of diagnosis may fluctuate between pathologists. Lipofuscin pigment in the cytoplasm of the inferior olivary cells may be called pigmentary atrophy by one observer, "normal for the age" by another, and ignored by a third. A Lewy body may be described as having a central core, a surrounding halo, or these may be absent. A variety of cellular phenomena may be dismissed without mention, but significance in terms of function is not known for mild neuronal pyknosis or swelling, pale

cytoplasm, displaced nucleus, satellitosis, etc. It is not sufficient to say these phenomena are found in normal brains; they may be pathologic under appropriate conditions. It would be just as proper to say that the bacillus of diphteria is not harmful because it is found in the throats of most normal persons.

Even when cellular or fiber tract changes are described, difficulties of language and definition interfere with the ability of the reader to understand what is said. When an author writes of "pigment atrophy of neurons", he may know clearly whereof he speaks, but most readers do not know how much pigment must be present to be so described. "Slight loss of cells", "thinning of ansa lenticularis", "reactive gliosis", "état criblé", and especially "état pre-criblé" often lack quantitative meaning, and are interpreted variously by different people. Description of a "pre-cribriform" state may be more suitable for fortunetellers than pathologists.

CLINICO-PATHOLOGIC CORRELATIONS

Here too difficulties arise. Davison (1940) indicated "although a few patients had unilateral tremor or rigidity, the lesions in the pallidum and substantia nigra were always bilateral". Many authors assume that the cause of tremor is the lesion in the substantia nigra but case 2 of McAlpine (1926) is a patient without tremor, although having a striking alteration of the substantia nigra. Furthermore, experimental destruction of the substantia nigra never produces tremor (Mettler, 1955). Cases of Parkinsons' disease have been reported in which the lesions were in the olivo-ponto-cerebellar system (Mathieu and Bertrand, 1929), or only in the inferior olivary nuclei (Keschner and Sloane, 1931). If these reports are accepted, injury to pallidum or nigra is not essential. Furthermore, the recent evidence from surgical or chemical pallidotomy indicates that relief from symptoms occurs with partial or complete destruction of the globus pallidus. Even the thalamus in which lesions have rarely been described may be partially destroyed with good symptomatic effects. Damage to basal ganglions or elsewhere by a single large lesion usually does not cause parkinsonian symptoms in man or other species, but Garcin et al. (1943) reported one case of a right fronto-callosal tumor, a hemi-Parkinson syndrome and relief of symptoms by removal of the tumor; Hardy and Stevenson (1957) described right-sided parkinsonism with cavitation in the left substantia nigra.

The significance of these discordant observations is difficult to assess. Some of the described lesions may bear no relation to the disorder. But it is recognized that a given lesion may cause symptoms which then are altered or disappear because of other lesions. Case VI described by Parkinson (1817) indicates that he knew of this effect when he described loss of tremor after hemiplegia but subsequent return of tremor in the arm and leg, "as their paralyzed state was removed".

The complexities of neurologic pathology, physiology and pathogenesis have become increasingly clear in our review of writings since James Parkinson described his syndrome in 1817. It is apparent that either morbid anatomists require more detailed and better controlled observations, or that we must look to new nechnics in our search for answers to the problems of this common disorder. Many forests have been gutted to create the paper on which much ink has flowed, but we may not be otherwise more advanced in basic understanding than when Horatio Wood in 1893 wrote "speculation has been rife as to the nature of the disease and various theories have been brought forward. None of these theories seem to me very plausible, and certainly, none of them are at all established".

SUMMARY

Arteriosclerosis and parkinsonism may be concurrent in the same patient, but evidence is lacking that one causes the other. Consideration is therefore given to postencephalitic and idiopathic parkinsonism. Postencephalitic parkinsonism was clearly de-

monstrated during the epidemic of lethargic encephalitis from 1914 to 1926. As each year passes since that time, it becomes increasingly difficult to diagnose new cases clinically. The only certain anatomic feature is inflammation. When inflammation subsides, it leaves doubt in its wake. As a result, although topographic differentiation has been described, most workers are unable to distinguish the two disorders histologically. Numerous conflicting reports have appeared concerning the site and nature of the lesions in these forms of Parkinson's syndrome. The substantia nigra is affected in most cases, the pallidum next most frequently, but rarely neither is involved; and other regions of the central nervous system may or may not be altered. Writers differ widely in their description of the lesions; observer bias and observer error may be factors in causing these heterogeneous accounts. The most common findings are nonspecific neuronal degeneration, neurofibrillary tangles, intracytoplasmic inclusions, demyelination and gliosis. The inclusions are more common in idiopathic paralysis agitans; the neurofibrillary changes more frequent in postencephalitic cases. Either of these findings, however, may occur in any case of parkinsonism, in other disorders, or in old age. An etiologic diagnosis is not possible on anatomic grounds except when inflammation is present. A definite pathologic picture therefore is not established either for idiopathic or postencephalitic parkinsonism.

RESUMEN

A pesar de que en el mismo paciente pueden coexistir arterioesclerosis y un síndrome parkinsoniano, no hay evidencia de una relación de causa a efecto entre ambos. Por esta razón se ha considerado el parkinsonismo postencefalítico y el idiopático. El parkinsonismo postencefalítico fue claramente demostrado durante la epidemia de encefalitis letárgica de 1914 a 1916.

Desde entonces hasta ahora se ha hecho cada vez más difícil diagnosticar clínicamente nuevos casos. La inflamación es la única prueba anatómica. Cuando ésta ha desaparecido no hay medio de hacer un diagnóstico con certeza. En consecuencia, aunque se han descrito diferencias topográficas, la mayoría de los autores no pueden distinguir histológicamente las dos formas. Con respecto al sitio y naturaleza de las lesiones en estas variedades del síndrome parkinsoniano, existen discrepancias en los numerosos trabajos publicados. En la mayoría de los casos la sustancia nigra está afectada, en orden de frecuencia le sigue el pallidum; pero es raro que uno de los dos no esté afectado y otras regiones del sistema nervioso central pueden o no estar alteradas. Los autores expresan grandes disparidades en la descripción de las lesiones; esto resulta de las opiniones personales y de errores de observación. Los hallazgos más comunes son degeneración neuronal no específica, placas neurofibrilares,, inclusiones intracitoplásmicas, desmielinización y gliosis. Las inclusiones son más comunes en la parálisis agitante idiopática; los cambios neurofibrilares son más frecuentes en los casos postencefalíticos.

Cada una de estas alteraciones, no obstante pueden aparecer en cualquiera de las formas de parkinsonismo, aun mismo en otras enfermedades o en la vejez. El diagnóstico etiológico no es posible del punto de vista anatómico, excepto cuando hay signos de inflamación. Por lo tanto no está establecido un cuadro anatomopatológico definido, tanto para el parkinsonismo idiopático como para el postencefalítico.

RESUME

Arteriosclerose et parkinsonism peuvent concourir dans le même malade, mais on n'a pas l'évidence que l'une soit la cause de l'autre. Donc, on considère le parkinsonism idiopathique et postencéphalitique. La dernière forme était demontrée particulièrement pendant l'épidémie d'encéphalite léthargique de 1914 à 1926. Après cette année,

il devient de plus en plus dificile de trouver de nouveaux cas, du point de vue clinique. La seule préuve definitive du point de vue anatomique est celle de la presénce de l'inflammation. Après que ce caractère soit disparu, il n'y a pas de moyende faire un diagnostic certain. Donc, quoique la diférenciation topographique a été décrite, la plupart des auteurs sont incapables de distinguer les deux entités histologiquement.

Plusieurs reports discordants ont été presentés sur l'endroit des lésions dans ces formes du Syndrome Parkinsonien. La substancia nigra est affectée dans la plupart des cas, le pallidum est le suivant en fréquence mais il est rare qu'aucun des deux ne soit affecté; il y a d'autres régions du système nerveux central qui peuvent être alterées. Les auteurs ne concurrent pas sur la description des lésions; leurs opinions particulières et toujours la possibilité d'erreurs individuelles peuvent être les facteurs causatifs de ces différences d'opinions. Les caractéristiques les plus communes sont la dégénération neuronal inespécifique, plaques neurofibrillaires, inclusions intracytoplasmiques, demielinization et gliose. Les inclusions sont plus fréquentes dans la paralysis agitans idiopathique; les altérations neurofibrillaires arrivent plus souvent dans la forme postencéphalitique. Chacune de ces alterations, cependant, peut se produire dans n'importe quelle forme de Parkinsonism ou même dans d'autres maladies, ou dans la viellesse. Un diagnostic étiologique n'est pas possible avec l'aspect anatomique, sauf quand il y a de l'inflammation. Une forme pathologique définitive, donc, n'est pas établie, ni pour la forme idiopathique, ni pour la forme postencéphalitique de la maladie de Parkinson.

ZUSAMMENFASSUNG

Arteriosklerose und Parkinsonismus können in Patienten zur gleichen Zeit auftreten, aber es liegen keine Beweise für ursachliche Zusammenhänge vor. Deshalb wurde Parkinsonismus als idiopathischer und postenzephalitischer Parkinsonismus abgehandelt. Während der Encephalitis lethargica Epidemie der Jahre 1914 bis 1926, konnte postenzephalitischer Parkinsonismus mit Sicherheit nachgewiesen werden. Von Jahr zu Jahr wurde es dann schwieriger neue Fälle zu diagnostizieren. Entzündung ist die alleinige, anatomisch entscheidende Veränderung. Sobald die Zeichen einer Entzündung zurückghen, müssen Zweifel auftreten. Demzufolge ist es meistens nicht möglich, die beiden Arten von Parkinsonismus histologisch zu unterscheiden, obwohl sie von der Topographie her unterschieden worden sind. Zahlreiche, einander widersprechende Beriche über Art und Sitz der pathologischen Veränderungen der verschiedenen Formen des Parkinsonismus Syndroms sind erschienen. In den meisten Fällen war die Substantia nigra befallen, das Pallidum kam an zweiter Stelle. Nur selten war keines der beiden Kerngebiete angegriffen. Andere Gebiete des Zentralnervensystems können, aber müssen nicht, neben den obengenannten Gebieten verändert sein. Verschiedene Verfasser beschreiben diese Veränderungen sehr unterschiedlich. Vorurteile und Fehler sind wahrscheinlich dafür verantwortlich. Die häufigsten pathologischen Befunde sind: unspezifische Neuronendegeneration, Neurofibrillengewirre, intrazytoplasmatische Inklusionskörper, Zerstörung des Myelins und Gliose. Inklusionskörper findet man häufiger im idiopathischen Parkinsonismus, während man Neurofibrillenveränderungen hauptsächlich in den postenzephalitischen Fällen beobachtet hat. Man kann jedoch jede dieser Veränderungen in beiden Arten von Parkinsonismus, in anderen Krankheitsbildern, und auch im alternden Gehirn antreffen. Eine Diagnose in Bezug auf die Ursache des Parkinsonismus kann nur auf Grund histologischer Befund gemacht werden, wenn Zeichen von Entzündung vorhanden sind. Es können deshalb keine spezifischen pathologischen Veränderungen im idiopathischen wie auch im postenzephalitischen Parkinsonismus beschrieben werden.

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Symptomatology and Medical Treatment of Parkinson's Disease

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It is now one hundred and forty years since James Parkinson published his extraordinarily clear description of the disease entity that bears his name. For reasons that are not too clear there has been a remarkable increase in interest in this condition since the ending of World War II, in 1945. The amount of published papers and textbooks that have appeared in the last fifteen years, especially in the last ten years, is nearly twice as large as the entire published material from 1817 until 1945. There are probably two main causes for this surprising growth of general interest in Parkinson's disease, both by physicians and by the general public.

The first is related to an apparent increase in the number of patients who have this condition in the various countries of the world, as compared to the known incidence, for example, in the middle of the last century. The second reason stems from the availability at the present time of a number of effective drugs that at least reduce the symptoms of this condition, and particularly the confirmed success, in selected victims of this disorder, of stereotactic surgery.

Incidence

It is not a simple task to determine with any degree of accuracy, the number of patients who have Parkinsonism in any country. Kurland has made a careful survey of one community, namely the city and surrounding country of Rochester, Minnesota, U.S.A. From these figures he has calculated that there must be at least 300.000 Parkinson's patients in the United States of America. Allowing for the presence of some undiagnosed cases, and others with such mild symptoms that they have not sought help, and combining this estimate of Kurland's with some others, such as our own (RSS) at the Massachusetts General Hospital, we can increase this number to 500,000 for the U.S.A. This represents an incidence of approximately 2,200 per million people, or 1 person in 450. This would mean that in any sizeable city where a medical school or medical center existed, with a population of one half to a million people, there would be at least 1000 patients in this area who had Parkinson's disease. The disease is therefore a common one. It is a challenge to the medical profession to find better treatment and management of this disorder.

At the Massachusetts General Hospital we have been especially interested in this disease since 1946. This has resulted in 15 years in our having approximately 1000 patients on our cards. From these we have determined, (see fig. 1) that the peak of age of onset is between 50 and 60 years, so it is very specifically a disease in the geriatrics group of people where other conditions, such as cancer, arteriosclerosis, arthritis and so forth also dominate the picture. Our data confirms an impression from a number of articles, that there are slightly more males than females, running 55 % male and 45 % females.

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Etiology

There is very poor evidence to date that the ordinary form of Parkinson's disease seen by most clinicians has any significant familial tendency. It is true that an occasional patient will have a relative, even a direct relative such as a sibling, or parent or a child who develops the disease as well, but the incidence of such situations in our own series in only 4 %, and at this rate one would attribute it to coincidence, i. e. both members of the same family who have the disorder probably had exposure to whatever the cause was.We have further evidence to support this in a search for twins in our series. Eleven of our patients had a twin, and five of the eleven were identical twins. In no twin, identical or other, was there any Parkinson's disease. This is strong evidence against it having a familial tendency. There are, however, groups of patients who have a different form of the condition to the ordinary one, where there is a familial relationship, and the most interesting group is on the Islands of Guam and Saipan in the Marianna group in the Pacific ocean, among the Chamorro natives. Here there is a strongly familial type of Parkinsonism with dementia and rather rapid development and early death. In some of these families there is also a familial form of amyotrophic lateral sclerosis. A few have both Parkinson's and the wasting of muscles. Except for this peculiar familial form of the disease in this one group of islands in the Pacific (See Kurland's report) we can state to our patients that Parkinsonism is not familial, and the children of patients who have it need not be concerned about developing it.

In the textbooks the disease is very frequently classified as postencephalitic, idiopathic and arteriosclerotic. We take exception to this classification, largely because there are so many exceptions in each group, and there is not any evidence that arteriosclerosis causes the disorder. We would prefer to call all cases idiopathic, but that satisfies no one. It would be more reasonable, we hold, to believe that some form of virus infection, such as the Spanish Influenza and Encephalitis Lethargica which swept the whole world from 1916 through 1927, produced as a sequella, sometimes many, many years later, the Parkinson's symptoms. With careful histories it is possible to identify a history of influenza of the Spanish world-wide epidemic type, or encephalitis in approximately 55 % of any group of patients. A more striking bit of evidence, however, is the fact that the present age of the Parkinson's patients in our group, and in that of other centers, is slowly rising, so that in 1961 the average age is 67 years; and some twenty years ago, the age was approximately 50. Furthermore, we have only one patient in our whole series that was born after the year 1929. If this concept is true that two-thirds of the cases at the present time are sequellae, delayed tremendously of course, from the world-wide epidemic, then the large number of patients with this disorder in the world today will slowly disappear as these die, and in ten or fifteen years time, the number of patients should be lessened. There seems to be some indication, at the present time, that this is what is happening, and we can even guess that by 1985 the number will have dropped close to the levels of 1910.

The symptoms associated with Parkinson's disease are much more diffuse than one would suppose from the early accounts of the disorder. The earliest symptom that patients complain of is an unexplainable, rather embarrassing loss of skill in the fingers of one hand. Usually within a year of noticing this, the patient may experience some fatigue and weakness of the muscles on one side of the body, and finally as an early symptom, under stress usually, a small amplitude resting tremor in one of the fingers of the hand will be noted. Approximately 80 % of all patients with this disorder first experience tremor or loss of fine motor skill in the fingers, as the earliest symptom. Rigidity, which is a very common finding in most patients, and is associated with tremor in the majority of patients, is probably present as early as the loss of finger skill and tremor, but it is not brought to the notice of the patient as clearly, and it may not be described as an early symptom. Other early symptoms that the patients may not notice, but which an alert physician

would certainly see, are loss of associated arm swing on walking, peculiar posture of the hand in repose, a beginning of loss of facial expression, and a staring of the eyes. There may also be detected by an alert observer a rather subtle awkwardness in starting off with any familiar pattern of movement, such as taking off one's coat, or getting into an automobile.

Another early group of symptoms that sometimes patients complain of, is a tendency to lose some of the automatic reflexes, such as blinking of the eyes, swallowing saliva whenever it accumulates in the mouth, and, when looking to the right or left, turning both eye and head simultaneously. The early loss of the swallowing reflex is associated with the appearance in the morning, by some patients, of some saliva on their pillow. This comes on well before the patients are conscious of drooling from their lips. Fatigability of the muscles in the hands and back and neck and legs and arms is a common symptom in Parkinson's disease, and is very frequently one of the early complaints of patients. Involvement of speech, so that it becomes monotonous, loses its volume so that it cannot be heard in groups of other people is usually not one of the early symptoms, but it is found in the majority after a few years. The characteristic regular resting tremor of 4 to 5 per second usually becomes more noticeable as the disease progresses, and is one of the prominent features of the disease in most textbooks.

While it is true that lesions in the basal ganglia associated with Parkinson's disease are not necessarily causes of any mental impairment or loss in intellectual acuity, a certain number of patients do complain of difficulty in thinking and memory, as an early symptom. As the disease progresses, the involvement of the very higher functions, which might be labeled congnitive functions, becomes more apparent. We would estimate that approximately 50 % of all patients with Parkinson's disease have evidence of impairment of the higher functions associated, for example, with making decisions and planning any ordinary venture, and being efficient in arranging one's day, and doing things that are ordinarily accomplished without difficulty. The level of such involvement in early cases of Parkinson's disease, within the first 5 years from the onset is not easy to measure, and an ordinary I. Q. test often shows no impairment. It is not easy to be certain that the symptoms of motor incoordination, rigidity that make it so difficult to carry out ordinary tasks, as well as the irritation and embarrassment of the resting tremor, may not contribute to inattention and distraction, so that the patients appear to be intellectually retarded or absent-minded with poor memory. We cannot, however, explain this intellectual involvement away on such grounds, because recent observations have shown that over 50 % of all patients with this disease have abnormalities in the electroencephalogram, which certainly would suggest that the higher brain functions are somewhat involved in these particular ones, and this is borne out in our study of this group.

As rigidity and tremor become more noticeable, and particularly when the symptoms appear on both sides of the body, the execution of normally learned motor patterns becomes more difficult and more awkward. Patients with this disease have great difficulty in doing simultaneously two motor acts, that they were quite able to do before the disease appeared. For example, reaching into their pocket to remove an object with the left hand, and opening a door with the right hand, become quite impossible. The only way they can achieve a normal performance in such tasks as dressing and so on, is to do each motor movement consecutively in a deliberate manner, requiring concentration and care in executing the act. This has led casual observers to feel that these people are obsessive or compulsive because of the deliberateness in arranging the motor performances that they face each day. However, this essentially is a very practical adaptation for a loss in the ability to do simultaneous motor acts of different types, and in no way is indicative of an obsessive, compulsive personality.

The symptomatology associated with tremor and rigidity of the limbs, the resting tremor, and the passive rigidity that is so characteristic of Parkinson's disease, is asso-

ciated of course with a loss of many cooperative and associated movements that make motor activity more efficient and easier to do; for example in squeezing with the fist, a normal person has learned, since he has been an infant, that the most efficient grip occurs when the wrist is semi-extended to an angle of 45 degress between the dorsal part of the fore-arm and the wrist. The Parkinson's patient loses this automatic learned extension of the wrist, to facilitate gripping, and he grips with the wrist out straight, or even in a flexed position. This means that the grip itself is much weaker, and the maintenance of it therefore, very inefficient.

One of the most devastating symptoms that occurs in some patients in the early part of their Parkinsonism, and in others only in the later stages, goes under the name of *akinesia*. This is defined as an inability to initiate motor acts, as well as an inability to sustain them at normal levels of performance and amplitude. For example, if a normal person is asked to do a repetitive act, such as squeezing a rubber bulb, he can do this without much effort or attention on his part, at intervals of every second, without much evidence of fatigue, over several minutes. The same thing occurs when he is walking. He takes long easy steps, without concentrating or requiring any special effort, in fact he may be conversing on a very complicated matter with a friend. The Parkinson's patient tends, on the other hand, with this symptom of akinesia, to start off with difficulty, and then as each motor act is completed, the efficiency becomes less and less and less; and finally the steps are only a fraction of their normal distance — the so-called petit pas of the Parkinson's. Diminution of amplitude not only occurs in walking, but in all types of voluntary muscular action, such as speaking, moving of the hands, limbs and head, so that all repetitive acts become diminished in their performance. In the case of speech, one starts off with a reasonably high volume, and it rapidly diminishes until only a whisper is heard. We do not know the reflexes or the pathology or the physiology that is disturbed in this symptom of akinesia, but it is a most disabling symptom. It is associated with an inability to change motion that is once started, so that the patient becomes frozen or locked in certain positions, and cannot get out of them. It becomes impossible, for example, to get out of a chair. When he does become erect with help, it is completely impossible for him to start to move, so that he must be dragged or pushed, involving the help of two people to get about. This goes by the name of freezing, but it is an integral part of the symptom complex called akinesia. Akinesia resembles fatigue of a rapid and pathological sort. Forexample, a patient with Parkinson's, squeezing a bulb attached to an ergograph, will diminish as quickly as if he had had a severe form of muscle exhaustion, such as myasthenia gravis. The difference between true fatigue and this symptom of akinesia is that the muscle itself is not involved, nor is the nerve to the muscle, but this is a peculiar deficit, not clearly understood, that is not associated with any break in continuity of motor nervous system. This is further complicated by another symptom that these same patients have, known as akinesia paradoxica. In such a situation, if any unusual stimulus occurs, of an emergency type, the patient may suddenly return to normal motor activity, and perform in a completely normal manner. This simply means that there are no breaks in long tracts, and that the neurological connections between the central nervous system and the performing muscles are intact, and can be brought into action if the stimulus is great enough. Examples are known to many physicians of patients who are nearly bed-ridden, in a building that catches afire who can, for a brief period of time, spring out of bed and run downstairs, and then at once return to their previous totally invalided state.

Secondary Symptoms in Parkinsonism

As a result of the presence of akinesia, and slowness in executing motor activities, fatigue and inefficiency in motor production, coupled with the embarrassment that they feel in the presence of strangers when they are eating a meal, for example, results in a number of symptoms that are secon-

dary to the primary disorder. First of these is a chronic, progressive malnutrition, or underweight. This is not emphasized in most textbooks, and is of particular concern because it usually leads to serious consequences. The Parkinson's patients as a rule do not consume more calories than normal for their body weight. Their tremor, while it produces a certain amount of activity of an involuntary type, is usually accompanied by much less voluntary use of their muscles, so that their actual metabolic levels are not higher than normal. In spite of this patients will tend to lose weight steadily. Perhaps it is only ten pounds a year, but in four or five years, such patients will go from a normal weight of, for example, 165 pounds down to 125 pounds, a loss of 40 pounds. The cause of this is quite obvious, they simply take in less calories than they need. They are not able, due to their akinesia, and their slowness of movement, their awkwardness and loss of fine finger movements, to clear their plate at the same time as the rest of the family, so they leave a good amount of food at each meal, that is not consumed. They are embarrassed because of their tremor, their tendency to spill food, and their drooling, and they try to get away from the table as soon as possible, particularly when they eat in public. An added complication is the medicine, which will be taken up under the section on therapy, so that their appetite is diminished, their normal salivary secretions which go with efficient consumption of food is reduced. In any case, the pattern in chronic weight loss occurs in nearly 75 % of all patients with Parkinson's disease. It is a very serious medical complication. The first reason to view this with concern is the fact that this chronic reduction in weight is accompanied by a loss of mineral substance from the bones, so that these bones become fragile, and show by X-ray true osteoporosis. As a second hazard along this same front there is the loss of muscle substance which ordinarily acts as padding for such bones as the femur and pelvis. The third factor, of course, in the weight loss is the weakness of the muscles that ordinarily support these bones. These three aspects of the Parkinson's malnutrition make the individual susceptible to minor falls. Such patients if they slip on a rug which would ordinarily produce only a bruise in their pre-Parkinson's days now sustain a fracture of the femur or pelvis, requiring immobility for several months, usually in a hospital, and sometimes starting them into an invalid state from which they never recover. This is very serious, even though under present orthopedic surgical procedures, such fractures can be pinned and other patients restored to mobility in a few months.

We have encountered as a symptom complex in a large group of Parkinson's patients, signs and complaints of gastrointestinal malfunction. Forty percent of our patients show some evidence of difficulty with their gastrointestinal tract. Some symptoms are only a little epigastric distress from time to time during the day, that doesn't respond to ordinary bicarbonate of soda, and may well be associated with a minor gastritis. We have encountered a number of active ulcers and ulcer-like syndromes in these patients that suggest that their gastrointestinal tracts are more vulnerable than in ordinary people, of their same age. The most disturbing symptom, however, is chronic constipation. The lack of a normal control of their voluntary muscles is one factor. There seems to be an intrinsic involvement due to the disease, so that the whole smooth muscle system, such as the intestinal tract behaves in a sluggish manner; there is certainly difficulty in normal evacuation of feces, even in the absence of drugs. In the treatment of the disease it is necessary to use a type of substance like belladona and atropine, and these drugs aggravate the tendency towards chronic constipation, which is present in so many of these individuals. The result of the drug treatment, plus the involvement by the disease with constipation, produces a very stubborn and difficult problem of bowel control. Some of these patients cannot adjust, even with proper cathartics, and they have to depend on enemas once or twice a week; but in general it is possible for the physician who understands this symptom complex to control it by an intelligent and vigorous use of laxatives, ingestion of plenty of fluids each day,

and an adequate diet with the proper amount of fluid-absorbing roughage in its structure. The seriousness of this symptom must be faced. We have investigated in the deaths of 100 patients of our series, and found that 6 of them were associated with partial or complete intestinal obstruction; and we have an additional 4 patients who have had intestinal obstruction operated on successfully and relieved; and they are still alive.

In the more advanced forms of the disease, due to the rigidity of the legs which interferes with normal circulation through the muscles in the lower limbs, and the tendency for the patients to remain immobile for long periods of time, often sitting in a chair, they develop edema of their feet. This at first is mild, and disappears when they lie down in bed. At other times it is attributed to their chronic heart or kidney disease, and appropriate antidiuretics or other medications are given. But as it advances it becomes more severe, the skin becomes involved and may break down with ulcers, the excessive edema which may run up as high as the mid tibia, adds to the weight of the feet, so that walking is most difficult and often impossible; patients are not able to get their shoes on, and this may eventually lead to a complete invalid state. Diuretics help a little, and if the cardiovascular and renal system are eliminated as a cause, which is the usual case, the only way that this kind of a complication of their disease can be reduced is to use vigorous physical therapy, several times a day, and keep the patients in a position where their feet can be elevated for two or three hours at a time, several times a day.

Medical Treatment

We have mentioned a number of symptoms concerned with the syndrome of Parkinson's disease, — tremor, rigidity, akinesia, loss of skilled motor movements, and fatigue. The treatment of these, by medication and by medicine in general, is not nearly as satisfactory as we would like. The most available drugs and combinations of drugs are built around the atropine series. If a drug such as hyoscine or stramonium is given in sufficient amount, it is possible to eliminate the rigidity as well as the tremor in the majority of patients with Parkinson's disease. *But* the side effects of such large doses are so severe that the patients will not tolerate them. Therefore an effective drug which would reduce tremor is eliminated, and the patient is back to where he was at the beginning. The formula of benefit over penalty, or $\frac{B}{P}$, should be emphasized here, because successful treatment by drugs depends entirely on a compromise where the drug is accepted, if it reduces tremor and rigidity and other symptoms, up to a point where the side effects are just tolerable and no further. The newer synthetic drugs, such as Artane. Kemadrin, Pagitane and Akineton should be started in small doses, two or three times a day, with meals, and increased every three or four days until the side effects begin to appear. If these side effects are very mild and not very unpleasant and can be tolerated, then the increase should be stopped, and the drug maintained at this point. If the side effects, which might be drying of the mouth, blurring of vision, increase in constipation and some tendency for poor memory, sometimes confusion at night, are not acceptable to the patient, then the level of the dose should be decreased slowly, until some compromise is reached. This is not an easy task to achieve. It requires extraordinary cooperation and understanding on the part of the patient, and a great deal of patience and attention on the part of the doctor. It is necessary frequently to have telephone conversations with the relatives or with the patient several times a week, in making such adjustments to new medicines. If the patient is nearby, it entails frequent visits with the doctor. There is no condition that requires a more individual and meticulous adjustment of medication for symptoms than does Parkinson's disease. I would categorically state that most of the failures of treatment by drugs, in this disease, are due to a lack of appreciattion of this point, by both the physician and the patient. It is true that even with the best cooperation and understanding and care on the part of the physician, it is not

always possible to achieve very satisfactory adjustments with drugs; but one can state that it is impossible to achieve any kind of adjustment if this kind of meticolous individual arrangements are not carried out. The drugs mentioned are mostly effective against rigidity. Another group of drugs, one of which is called Parsidol, is a phenothiazine that does not produce the symptoms or increase the tremor; and another called Pacatal can be effectively used against tremor. These drugs, again, must be started in very small doses, and slowly increased until side effects appear. If these side effects are minimal the dosage level should be kept at this point; if the side effects are not tolerable, the dosage must be reduced. Combinations of the atropine type of drugs and these two phenothiazines are sometimes necessary, where there is both rigidity and tremor to contend with.

Patients with Parkinson's must frequently get other drugs in order to be made comfortable. If they are drowsy and dull as the result of their medicine, or as a result of their disease, amphetamines and Ritalin and other stimulant drugs have to be used. If they have difficulty in relaxing, if they are tense, nervous and agitated, then sedatives and tranquilizers have to be added to the medicine they are on. Some patients with this disease have an extreme difficulty in sleeping at night, which requires adjusting them to a combination of hypnotics and sedatives before they go to bed, which will not leave them dull and apathetic and confused the next morning. A small dose of Nembutal such as 50 mg. added to Meprobamate or Benadryl may be a helpful combination. Small doses of Chloral hydrate repeated once, can be used. As the patients become older, they become more sensitive to drugs that are available for treatment of their symptoms. One sometimes reaches the state where the patient cannot take even the smallest amount of a drug such as Artane, without becoming confused or even hailucinated or develop symptoms of urinary retention. In such cases the drugs cannot be given. A number of patients in their seventies and eighties are better off with no medication, rather than be made worse by complicated schedules.

Physiotherapy in all of its forms is very helpful in making patients with this disease more comfortable. No specific program can be recommended. Each individual has to work it out by himself, in relation to the availability of the physiotherapist, and his own financial resources, but in general one can say that the more physiotherapy he can get each week, the better off he will be. Physiotherapy should be directed at specific symptoms that the patient presents. This usually entails some specific contact on the part of the physician with the physiotherapist, who can be much more efficient if he is directed. For example, if the main symptoms of the patient are tremor without much rigidity or difficulty in walking, physiotherapy cannot do very much. It is true that some massage and possibly heat treatments will make a person more relaxed, but this is only a transient effect, and it is hardly worth the time of the patient, going out of his way to the therapist's office or institution. On the other hand, if there is rigidity present, and if there is difficulty with the walking, particularly difficulty in posture, so that the person walks stooped over, the physiotherapist can do a great deal. Passive extension, not to a point of causing pain but stretching the muscles, is a very important way of reducing rigidity and enabling the patient to use his voluntary muscles more efficiently.Posture exercises, gait training, exercises in breathing, stretching the back and neck muscles, are all very important. It is very difficult for a patient to do these himself, particularly in patients with Parkinson's disease, suffering from various degrees of akinesia. A session lasting anywhere from half an hour to forty-five minutes, under the competent direction of a good physiotherapist can be supplemented by home exercises, led possibly by a spouse or a nurse, or someone else, so that the patient will do them several times a day. This will see that the program is sufficiently carried out, and it may reduce the necessity of seeing the physiotherapist more than twice a week. There are a number of physicians who feel that physiotherapy is the main structure of a rehabilitation program to get patients with Parkinson's back to

doing their ordinary tasks and even back to work, but the evidence is very unconvincing that this is true. I certainly would go along with the feeling that physiotherapy, if it is properly done and does not fatigue the patient or overload him with severe burdens in travel and financial outlay, is a very good thing, and as stated in the previous paragraph, the more frequent the sessions are, the better.

It would not be intelligent to cover the general subject of medical treatment of Parkinson's disease without referring specifically to psychotherapy. A large number of patients with this condition have reactive depressions to their illness, some of them are in deep depressions of an endogenous sort, and some have other symptoms of mental disturbance, as well as emotional difficulties. Most of the time an intelligent and mature general physician can reassure patients with this disorder, take care of a modest amount of depression and other psychiatric symptoms without the necessity of having the patient followed by a psychiatrist. There are however, situations where a professional psychiatrist is essential. Some of the patients with considerable depression will improve with interviews directed by a competent psychiatrist; a few may require treatment with electric shock. Some patients with mild depressions can be helped by the antidepressive drugs such as Tofranil and even some of the amphetamines are helpful. In general the treatment of depression with drugs has to be supplemented by some form of regular psychotherapy. As Parkinson's disease progresses, particularly in the elderly, signs of organic mental disturbance usually complicate the picture. Here there is not much that can be done with psychotherapy. Some of these patients in their seventies may also be depressed. In general one encounters disturbance in memory and attention, confusion and lack of interest in their surroundings, and these sometimes are improved by one or two psychiatric interviews, but it requires a man who is familiar with this syndrome of Parkinson's disease.

There are a number of substances that are definitely contraindicated in the treatment of Parkinson's disease, and it seems worth while to have a special paragraph devoted to this particular problem. The phenothiazines, with the exception of Parsidol and Pacatal, previously mentioned, in general produce symptoms and signs of Parkinsonism in normals, if they are taken in large enough amounts, and *invariably* increase some of the symptoms of the disease if they are given to patients with Parkinson's. It is not emphasized in most of the brochures supplied by the manufacturers of these compounds that they should not be used in the treatment of depression or confusion or even of paranoid ideas in patients who have Parkinson's disease. Such drugs as Chlorpromazine, Compazine, Sparine, Stelazine and others of the phenothiazines with chloride or fluoride radicals should not be used at all in the program of therapy in this condition. Reserpine drugs also are usually followed by increasing side effects in patients with Parkinson's disease, when they are used to combat high blood pressure. Phenobarbital and amytal are sometimes given to patients with this condition as a hypnotic or sedative, and they usually increase the lethargy and dullness that such patients complain of. The quick-acting barbiturates like Nembutal or Seconal are better tolerated by patients with Parkinson's disease.

Sometimes a physician is tempted to add thyroid extract to the drugs given to patients with Parkinson's disease, to combat the slowness, the staring and loss of facial expression which might in some ways resemble hypothyroidism. If this drug is given in small amounts (30 mg. daily for example) to a person who has normal metabolic levels, it probably will not increase the metabolism in any significant way, and perhaps it does not do any harm. In general, however, thyroid is contra-indicated in most patients with Parkinson's disease, unless there is definite evidence of a considerable degree of hypothyroidism, by proper laboratory tests, such as a radio-active iodine uptake, or the protein bound iodine level, and not the basal metabolic rate. In our own experience we have found that some patients with continual slow loss of weight, a lot of tremor and restlessness benefit by the opposite form of treatment,

provided their metabolic levels are in the upper ranges of normal, i. e., depressing their metabolism by radio-active iodine in small amounts. It allows their metabolism to slow down, and their weight to be restored with the same amount of calories that they are taking. We have had about thirty patients out of the 100 that we have tested, who have had their metabolism slightly lowered in this manner, and have responded favorably. Indeed, there are a few cases of frank hyperthyroidism with Parkinson's disease that have improved to such a degree that the anti-Parkinson's medicine could be withdrawn when their metabolism was reduced to a low normal value. I do not recall any patient who was specifically harmed by taking small amounts of thyroid, but I am quite certain that I can recall no patient that was benefited by such a medicine.

In working out the medical schedule of patients with Parkinson's disease, arranging their general supervision and management, one must keep in mind at the present day, that suitable patients ought to be given an opportunity of consulting a neurosurgeon, to see whether a lesion in the thalamus is

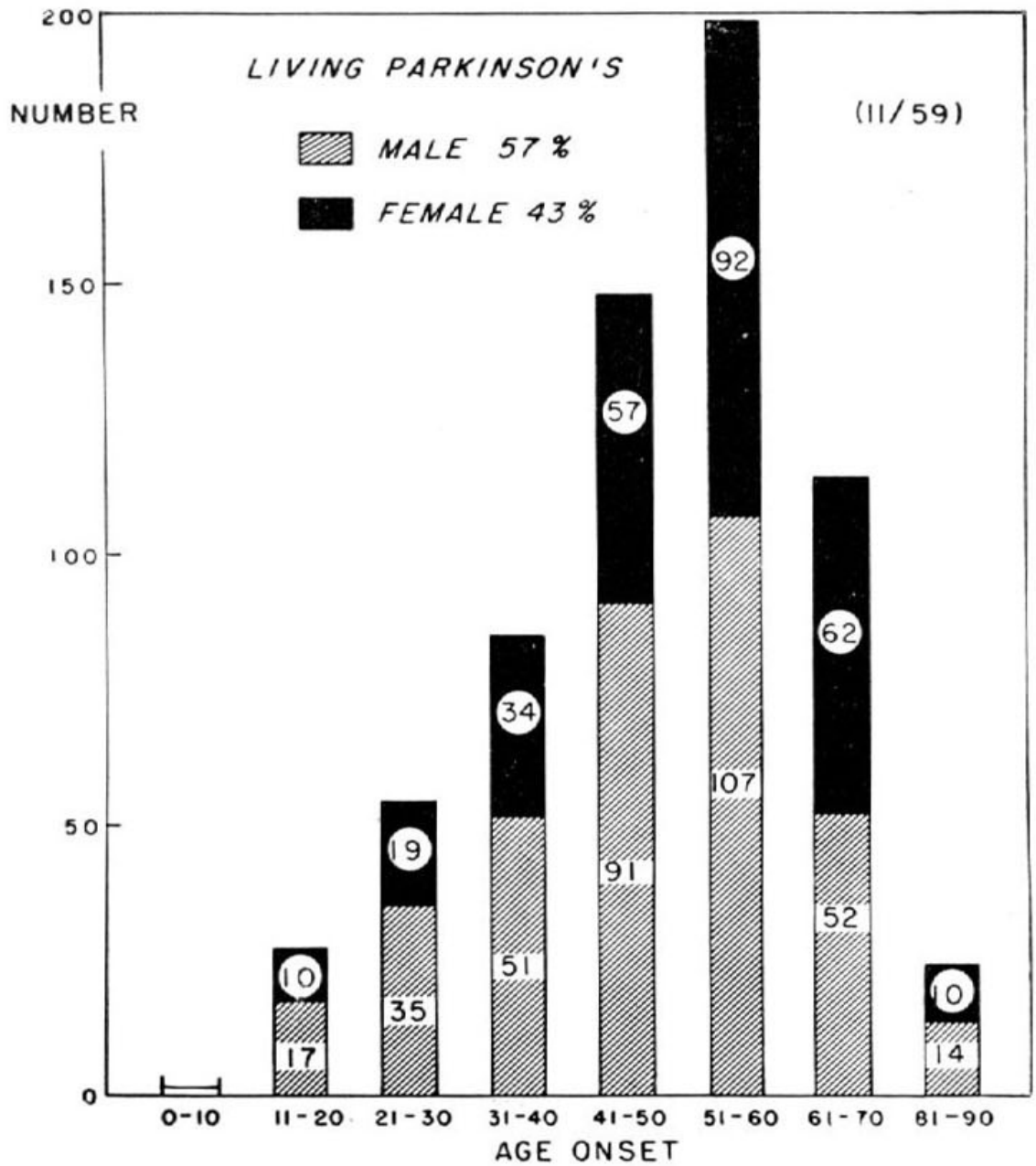

Figure 1. — Incidence versus age.

indicated and would be advisable in this particular situation. We feel at the present time, that about one patient in ten would benefit from a neurosurgical attack on his disease. Relief of tremor and rigidity on the contralateral side from the lesion, would make the whole problem of medical management and treatment in the future much easier. The selection of proper patients for surgery, the various techniques that could be done, the evaluation of the results, is not within the scope of this particular article. One can, however, hardly write on the medical treatment of Parkinson's disease without keeping in mind the fact that there is at the present time a successful form of surgical intervention.

When the disease of Parkinson's has been firmly diagnosed so that there is no question about its presence, the physician responsible for this patient has taken on a problem that is going to be with him as long as he and this patient are in the same area. Since there is no cure, and the general pattern of the disease is one of either slow or rapid progression, frequent contacts between the patient and his physician are essential. Excellent medical supervision, a type of simple but efficient psychotherapy and support must be the background for this management. The use of drugs, mechanical aids, physiotherapy are all part of an integrated program of management. No two patients are alike, and we really have a challenge to ingenuity and persistence that the physician has to face here, if his patients are going to be benefited.

SUMMARY

There has been a remarkable increase in interest in this condition since the ending of World War II, in 1945.

Kurland, has calculated that there must be at least 300.000 Parkinson's patients in the United States of America.

We have determined, that the peak of age of onset is between 50 and 60 years, there are slightly more males than females, running 55 % male and 45 % females.

There is very poor evidence to date that the ordinary form of Parkinson's disease seen by most clinicians has any significant familial tendency. There are, however, groups of patients who have a different form of the condition to the ordinary one, where there is a familial relationship, and the most interesting group is on the Islands of Guam and Saipan in the Marianna Group in the Pacific Ocean, among the Chamorro natives. Here there is a strongly familial type of Parkinsonism with dementia and rather rapid development and early death. In some of these families there is also a familial form of amyotrophic lateral sclerosis.

In the textbooks the disease is very frequently classified as postencephalitic, idiopathic and arteriosclerotic. We take exception to this classification, largely because there are so many exceptions in each group, and there is not any evidence that arteriosclerosis causes the disorder.

The earliest symptom that patients complain of is an unexplainable, rather embarrassing loss of skill in the fingers of one hand. Approximately 80 % of all patients with this disorder first experience tremor or loss of fine skill in the fingers, as the earliest symptom. Rigidity, is associated with tremor in the majority of patients.

Another early group of symptoms that sometimes patients complain of, is a tendency to lose some of the automatic reflexes, such as blinking of the eyes, etc. Fatigability of the muscles in the hands and back and neck and legs and arms is a common symptom in Parkinsons's disease. The characteristic regular resting tremor of 4 to 5 per second usually becomes more noticeable as the diseases progresses.

A certain number of patients do complain of difficulty in thinking and memory, as an early symptom.

We would estimate that approximately 50 % of all patients with Parkinson's disease have evidence of impairment of the higher functions of the brain. Recent observations have shown that over 50 % of all patients with this disease have abnormalities in the electroencephalogram.

One of the most devastating symptoms

that occurs in some patients goes under the name of akinesis. This is defined as an inability to initiate motor acts, as well as an inability to sustain them at normal levels of performance and amplitude.

There are a number of symptoms that are secondary to the primary disorder. First of these is a chronic, progressive malnutrition, or underweight. Forty percent of our patients show some evidence of difficulty with their gastrointestinal tract. They develop edema of their feet.

For treatment, the most available drugs and combinations of drugs are built around the atropine series. The newer synthetic drugs, such as Artane, Kemadrin, Pagitane and Akineton should be started in small doses, two or three times a day, with meals, and increased every three or four days until the side effects begin to appear.

There is no condition that requires a more individual and meticulous adjustment of medication for symptoms than does Parkinson's disease.

The drugs mentioned are mostly effective against rigidiy. Another group of drugs, one of which is called Parsidol, is a phenothiazine that does not produce the symptoms or increase the tremor; and another called Pacatal can be effectively used against tremor.

If they are drowsy, amphetamines and Ritalin and other stimulant drugs have to be used. If they are tense, nervous and agitated, then sedatives and tranquilizers have to be added the medicine they are on.

Physiotherapy in all of its forms is very helpful in making patients with this disease more comfortable. Most of the time an intelligent and mature general physician can reassure patients with this disorder, take care of a modest amount of depression and other psychiatric symptoms, without the necessity of having the patient followed by a psychiatrist.

Such drugs as Chlorpromazine, Compazine, Sparine, Stelazin and others of the phenothiazines with chloride or fluoride radicals should not be used at all in the program of therapy in this condition.

In working out the medical schedule of patients with Parkinson's disease, arranging their general supervision and management, one must keep in mind at the present day, that suitable patients ought to be given an opportunity of consulting a neurosugeon, to see whether a lesion in the thalamus is indicated and would be advisable in this particular situation.

RESUMEN

Desde que terminó la 2ª guerra mundial en 1945, se ha producido un notable aumento en el interés sobre el Parkinsonismo.

Kurland ha calculado que existen por lo menos 300.000 pacientes parkinsonianos en los Estados Unidos.

La edad de comienzo de la afección está entre los 50 y los 60 años.

Hay ligeramente más hombres que mujeres, siendo la proporción 55 % hombres y 45 % mujeres.

Es muy poco probable que la forma habitual del parkinson tenga tendencia familiar.

Existen sin embargo grupos de pacientes con una forma especial de enfermedad en la cual se observa un vínculo familiar y el más interesante está en las islas de Guam y Saipan, en el grupo de las Marianas en el Pacífico, entre los nativos chamorros. Aquí hay un tipo de parkinsonismo fuertemente familiar con demencia y una rápida evolución hacia la muerte. En algunas de estas familias se observa también una forma familiar de esclerosis lateral amiotrófica.

En los textos la enfermedad es clasificada con frecuencia en 3 grupos: postencefalítico, idiopático y arterioesclerótico. Nosotros no seguimos esa clasificación, principalmente porque hay muchas excepciones en cada grupo y porque no existe ninguna evidencia de que la arterioesclerosis produzca la enfermedad.

El síntoma más precoz de que se quejan los enfermos, es una inexplicable y molesta falta de habilidad en los dedos de la mano. Aproximadamente el 80 % de todos los pacientes con esta afección, experimentan al principio temblor o pérdida en la destreza para los movimientos finos de

los dedos. La rigidez está asociada con el temblor en la mayoría de los casos.

Otro sistema precoz que a veces da lugar a queja de los pacientes es la tendencia a perder algunos de los reflejos automáticos tales como el parpadeo, etc.

La fatigabilidad de los músculos de las manos, la espalda, la nuca y en las piernas y brazos es un síntoma común en la enfermedad de Parkinson. El temblor de reposo característico, de una frecuencia de 4 ó 5 por segundo, habitualmente se hace más perceptible a medida que la enfermedad progresa.

Un cierto número de pacientes se queja de dificultad para pensar y para recordar. Estimaríamos que aproximadamente un 50% de todos los parkinsonianos evidencian perturbaciones en las funciones cerebrales superiores.

Observaciones recientes han demostrado que más del 50 % de los pacientes tienen anormalidades en el electroencefalograma.

Uno de los síntomas más perturbadores es la llamada aquinesia. Puede definirse como la dificultad para iniciar actos motores y la imposibilidad para mantenerlos durante su ejecución en niveles normales.

Hay un número de síntomas que son secundarios al desorden primario. en primer término mencionaremos una desnutrición progresiva crónica. El 40 % de nuestros pacientes evidenciaron dificultades en el aparato digestivo. Es frecuente el edema en los pies.

En lo que se refiere al tratamiento médico, la mayoría de las drogas y combinaciones de drogas corresponden a la serie atropínica. Las drogas más nuevas, tales como el Artane, el Kemadrin, el Pagitane y Akineton deben ser iniciadas a dosis pequeñas, dos o tres veces por día con las comidas y aumentadas cada 3 ó 4 días, hasta que los efectos colaterales comiencen a producirse.

No hay afección que requiera un ajuste especial de la medicación más meticulosamente hecho para cada individuo, que la enfermedad de Parkinson.

Las drogas mencionadas anteriormente son sobre todo efectivas contra la rigidez. En otro grupo de drogas, señalaremos el Parsidol, que es una fenotiazina, y el Pacatal, ambas pueden ser efectivamente usadas contra el temblor.

Si existen atontamiento o depresión pueden ser utilizadas las anfetaminas y el Ritalin. Si el paciente está tenso y agitado, deben agregarse sedantes y tranquilizantes.

La fisioterapia en todas sus formas es útil y hace más llevadera esta afección.

Por lo general un médico inteligente puede dar apoyo moral a estos pacientes, cuidar una depresión que no sea muy severa, así como otros síntomas psíquicos sin necesidad de recurrir a un psiquiatra.

En la terapéutica de esta afección deben ser eliminadas la Clorpromazina, la Compazina, la Esparina, Estelazina y otras fenotiazinas con radicales cloruros o fluoruros.

Estos pacientes deben consultar al neurocirujano para decidir si está indicada la cirugía estereotáxica.

RESUME

Depuis la fin de la deuxième guerre mondiale en 1945, on a noté un regain d'intérêt pour la maladie de Parkinson.

Kurland a calculé qu'il éxiste au moins 300.000 Parkinsoniens au États Unis.

Le début de l'affection se situe entre 50 et 60 ans, atteignant légèrement plus l'homme que la femme: 55 % chez l'homme 45 % chez la femme.

Il y a peu de probabilité d'une influence familiale dans la forme commune de la maladie.

Il éxiste pourtant des groupes de patients présentant une forme particulière de la maladie, chez lesquels s'observe un lien familial. Le groupe le plus intéressant se situe dans les îles de Guam et de Saïpan, dans le Pacifique, chez les natifs Chamorros. On trouve là, un type de Parkinsonisme, fortement familial avec démence et évoluant rapidement vers la mort. Dans quelques'unes de ces mêmes familles on recontre également une forme familial de sclérose latérale amyotrophique.

Dans les textes, la maladie est fréquemment classée, en 3 divisions: postencephali-

tique, idiopathique et artériosclerotique. Nous ne suivons pas cette classification, parce qu'il y a de nombreuses exceptions dans chaque groupe et qu'il n'est pas évident que l'artériosclérose soit une cause de la maladie.

Le symptôme le plus précoce, dont souffrent les malades est un manque d'adresse inexplicable et gênant dans les doigts de la main. Environ 80 % de tous les malades présentant au début un tremblement et une perte d'habileté dans les mouvements des doigts. La rigidité est associée avec le tremplement dans la majorité des cas.

Un autre symptôme précoce, dont se plaignent les patients est la tendence à perdre quelques un des reflexes automatiques comme le clignotement de la paupière, etc.

La fatigabilité des muscles de la main, de l'épaule, de la nuque, des jambes et des bras est un symptôme banal de la maladie de Parkinson. Le tremblement de repos est caractéristique, avec une fréquence de 4 à 5 par seconde. Il devient habituellement plus perceptible au fur et à mesure des progrès de la maladie. Certains patients se plaignent de difficultés pour penser et se souvenir.

Nous estimons qu'environ 50 % de tous les Parkinsonniens sont atteints de troubles des fonctions cérébrales supérieures. Des observations récentes ont démontré, chez 50 % des patients, des anomalies de l'electroencephalogramme. Un des symptômes les plus gênants est l'akinésie, que l'on peut définir comme une difficulté de commencer des actes moteurs et l'impossibilité de les maintenir pendant leur éxécution à des niveaux normaux.

D'autres symptômes sont secondaires au désordre primaire, d'abord nous citerons une dénutrition chronique progressive, 40% de nos patients ont montré des complications digestives. L'oedéme des pieds est fréquent.

En ce qui concerne le traitement médical, la majorité des drogues et associations de drogues correspondent à la série atropinique. Les produits plus récents, comme l'Artane, la Kemandrin, le Pagitan et l'Akineton doivent être administrés inicialement à doses petites, deux à trois fois par jour avec les repas, puis augmentées chaque 3 ou 5 jours jusqu'à apparition des effects secondaires.

Aucune affection ne nécessite comme la maladie de Parkinson un ajustement aussi particulier et méticuleux de la médication pour chaque individu.

Les drogues antérieurement citées sont surtout actives contre la rigidité. Dans un autre groupe, nous mentionnerons le Parsidol dérivé phénotiazinique et le Pacatal, les deux sont actives contre le tremblement.

En cas d'abêtissement ou de dépression on peut utilisér les amphétamines et la Ritalin. Si le patient est en état de tension et agité on doit ajouter des sédatifs et des tranquilisants.

La physiothérapie sous toutes ses formes est utile et rend plus supportable cette affection.

En général un médecin compréhensif peut apporter un appui moral à ses patients et traiter, sans l'aide d'un psychiâtre, les états de dépression pas trop sévères et les autres manifestations psychiques.

De la thérapeutique de cette affection, on doit éliminer la chlopromazine, la Compazine, la Sparine, et autres phénotiazines avec un radical chlorure ou fluorure.

Les patients doivent consulter le neuro chirurgien pour décider de l'opportunité de la chirurgie stéréotaxique.

ZUSAMMENFASSUNG

Es existiert eine sehr grosse Zunahme des Interesses fuer diese Krankheit seit Ende des 2. Weltkrieges im Jahre 1945.

Nach Kurland gibt es wahrscheinlich mindestens 300.000 Faelle von Parkinson in den U.S.A.

Die Krankheit beginnt in der grossen Mehrzahl der Faelle zwischen 50 und 60 Jahren und es werden etwas mehr Maenner als Frauen befallen (ca 55 % Maenner und 45 % Frauen).

Es besteht wenig Wahrscheinlichkeit fuer

die Annahme, dass die gewoehnliche Form der Parkinson'schen Krankheit eine familiaere Tendenz hat. Es gibt jedoch Gruppen von Patienten, welche eine verschiedene Form der Krankheit haben, bei welcher diese familiaere Tendenz besteht. Die interessanteste Gruppe in dieser Hinsicht findet sich auf den Inseln von Guam und Saipan und in der Marianna Gruppe des Pazifischen Ozeans unter den Eingeborenen von Chamorro. Hier existiert ein familiaerer Typ von Parkinson mit Demenz, rascher Verschlimmerung und fruehem Tod. Bei einigen dieser Familien findet sich auch eine familiaere Form von amyotrophischer Lateralsklerose.

In den Lehrbuechern wird der Parkinson sehr oft beschrieben als postenzephalitisch, idiopatisch oder arteriosklerotisch bedingt. Wir nehmen diese Klassifizierung nur mit Vorbehalt an, vor allem weil in jeder Gruppe so viele Ausnahmen bestehen und weil keine Beweise vorhanden sind, dass die Arteriosklerose die Krankheit verursachen kann.

Das frueheste Krankheitssymptom ist ein unerklaerlicher, sehr laestiger Verlust der Fingerfertigkeit einer Hand. Ungefaehr 80 % der Patienten zeigen als erstes Symptom ein Zittern oder den Verlust der feinen Fingerfertigkeit. Zittern ist meist assoziert mit Rigiditaet.

Eine andere Gruppe von Symptomen ist die Tendenz, die automatischen Reflexe zu verlieren, wie z. B. das Schliessen der Augenlider. Ermuedbarkeit der Muskeln der Hand, der Arme und Beine, des Halses und des Rueckens ist ein haeufiges Symptom der Parkinson'schen Krankheit. Das charakteristiche Zittern in Ruhe (4-5 mal pro Sekunde) wird meist manifest wenn die Krankheit fortschreitet.

Eine gewisse Zahl von Patienten zeigen als erstes Krankheitssymptom Schwierigkeiten im Denken und in Gedaechtnis.

Wir schaetzen, dass ungefaehr 50 % aller Parkinson-Patienten Zeichen con Steorung der hoehern Gehirnfunktionen zeigen. Moderne Untersuchungen zeigten, dass ueber 50 % der Faelle Anormalitaeten im EEG aufweisen.

Eines der schlimmsten Symptome der Krankheit, das bei einigen Faellen auftritt, wird als Akinese bezeichnet: dies ist die Unfaehigkeit, motorische Akte zu beginnen und sie aufrecht zu erhalten auf einem normalen Niveau.

Es treten eine Menge von Symptomen auf, welche sekundaerer Natur sind als Folge der primaeren Stoerung. So sieht man z. B. eine chronische, progressive Unterernaehrung und Gewichtsabnahme.

40 % unserer Patienten zeigen Stoerungen von Seiten des Gastro-intestinaltraktes. Sie leiden auch an Oedemen der Fuesse.

Was die Behandlung der Krankheit anbetrifft, so sind die meisten der ueblichen Medikamente und medikamentoesen Kombinationen aufgebaut auf dem Atropin. Die neueren synthetischen Praeparate wie Artane, Kemadrin, Pagitan und Akineton muessen anfangs in kleinen Dosen gegeben werden, 2 bis drei Mal taeglich, mit den Mahlzeiten und die Dosis muss alle 3-4 Tage gesteigert werden bis Nebenerscheinungen auftreten.

Es gibt keine andere Krankheit, die in solchem Mass eine individuelle und metikuloese Dosierung braucht wie die Parkinson'sche Krankheit. Die oben erwaehnten Medikamente sind vor allem wirksam gegen die Rigiditaet. Eine andere Gruppe von Medikamenten, zu welchen Parsidol gehoert, ist ein Phenotiazin, welches das Zittern nicht steigert; ein anderes Medikament heisst Pacatal und dieses kann mit Erfolg gegen das Zittern verwendet werden.

Wenn die Kranken schlaefrig sind, kann man ihnen Amphetamin, Ritalin oder andere stimulierende Medikamente geben. Wenn sie nervoes oder erregt sind, muss man Beruhigungsmittel oder 'tranquilizers' zur ueblichen Medikation hinzufuegen.

Physiotherapie in allen Formen ist sehr nuetzlich, um den Kranken ihr Leiden ertraeglicher zu gestalten. Ein guter und erfahrener allgemeiner Arzt kann meist die Patienten mit Parkinson behandeln, kann ihre Depression bekaempfen und auch ihre andern psychiatrischen Beschwerden, ohne dass die Notwendigkeit besteht, dass der Patient psychiatrische Betreuung braucht.

Medikamente wie Chlorpromazin, Compazine, Sparine, Stelazin und andere Phenotiazinpraeparate mit Radikalen von Chlor

oder Fluor sollten nicht verwendet werden.

Bei der medizinischen Behandlung der Parkinsonkranken sollte in Betracht gezogen werden, dass geeigneten Patienten die Gelegenheit gegeben werden sollte, einen Neurochirurgen zu konsultieren, um sich zu vergewissern, ob ein Eingriff am Thalamus indiziert ist.

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Traitement Chirurgical de la Maladie de Parkinson

Remarques méthodologiques et technique chirurgicale

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Le traitement neuro-chirurgical des syndromes parkinsoniens connait un développement considérable depuis l'introduction dans la pratique neuro-chirurgicale courante des méthodes stéréotaxiques qui permettent d'atteindre avec précision différents points des noyaux gris centraux et d'y pratiquer des lésions localisées.

Ces interventions visent à modifier l'état fonctionnel de circuits neuronaux complexes, impliqués dans le contrôle et la régulation de l'activité motrice et du tonus, beaucoup plus qu'à détruire d'hypothétiques centres sous-corticaux ou même exclure un foyer pathologique irritatif.

Cette orientation nouvelle d'une véritable chirurgie fonctionnelle du parkinson s'adresse principalement aux afférences. Elle succède aux interventions à visée plus directement anatomique qui portaient sur l'effecteur à differénts niveaux, cortical, pédonculaire, médullaire, au prix d'une paralysie régressive dans des proportions variables.

Il a pu être ainsi admis lors des interventions stéréotaxiques portant sur le globus pallidus ou l'anse lenticulaire qu'une atteinte même discrète du faisceau pyramidal était indispensable à la guérison et à la permanence du résultat.

L'expérience a cependant montré d'une part, qu'un effet thérapeutique indiscutable pouvait être obtenu en l'absence de tout signe de lésion pyramidale, d'autre part que les divers éléments du syndrome parkinsonien étaient inégalement modifiés et de façon inconstante par certaines petites lésions pallidales, le tremblement paraissant plus difficile à réduire de façon durable que l'hypertonie.

Les premières tentatives stéréotaxiques visaient exclusivement le pallidum dans le but d'interrompre principalement les voies efférentes descendantes.

Au cours de ces dernières annés, deux ordres de faits ont modifié l'orientation du traitement chirurgical du Parkinson:

a) L'étude anatomique, reprise par Hassler(1), du thalamus et des noyaux lenticulaires, et de leurs connexions a conduit cet auteur à préciser l'importance des relais thalamiques sur les circuits pallido-corticaux, au niveau du noyau ventral antérieur, et surtout de la partie basse et antérieure du noyau ventral latéral (v.o.a.). Ces efférences ascendantes du globus pallidus parviennent en majorité à l'aire prémotrice.

b) Une série de recherches expérimentales cherchant à reproduire le tremblement parkinsonien ont mis en évidence, parmi d'autres structures, l'importance du pédoncule cérébelleux supérieur dont les influ sont projetés par le noyau rouge, puis par le noyau ventral latéral du thalamus vers le cortex moteur précentral (aire 4).

Les épreuves de stimulation chez l'homme de ce noyau thalamique, ont également montré son rôle dans le contrôle du tremblement parkinsonien (*Riechert-Hassler*).

En conséquence, des neurochirurgiens ont réalisé la destruction de ces diverses structures nucléaires thalamiques dans le but de modifier globalement les afférences corti-

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cales pathologiques provenant des formations sous-corticales ou cérébelleuses, impliquées dans le contrôle de la motricité. Cependant de nombreux auteurs restent fidèles, avec des résultats appréciables, aux lésions du globus pallidus dont certaines voies efférentes sont d'ailleurs directement descendantes vers les noyaux sous-thalamiques et la formation réticulée.

Nous ne voulons pas discuter ici les mécanismes possibles de l'action des lésions thérapeutiques ou les problèmes de l'organisation du système moteur. En effet, il nous semble que les conclusions tirées de l'expérience stéréotaxique sont souvent aléatoires ou reposent sur des bases non suffisamment solides.

Pour toutes recherche valable dans ce domaine, trois critères méthodologiques nous paraissent fondamentaux.

1. *Bases anatomiques de la localisation des points-cibles.*

Nous avons déjà à plusieurs reprises insisté sur la très grande variabilité des dimensions et des rapports spatiaux des noyaux gris centraux(2). Les repères osseux n'étant pas en relations suffisamment cons-

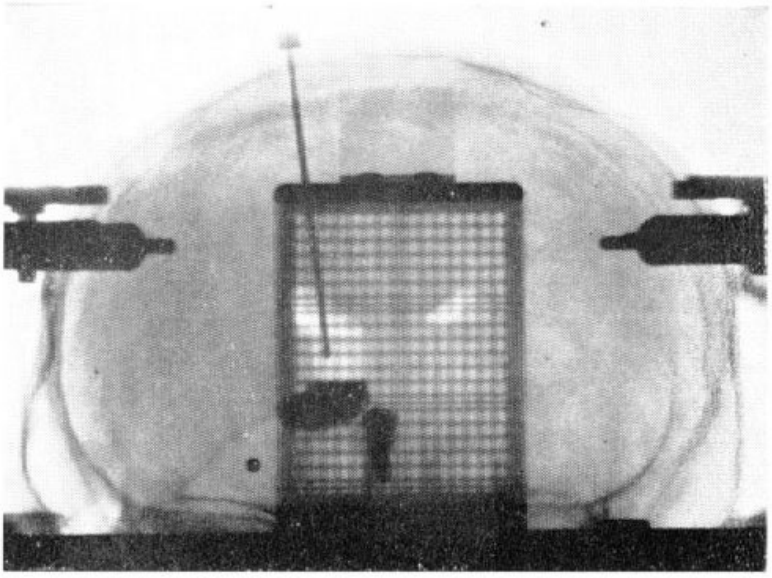


Figure 1 a

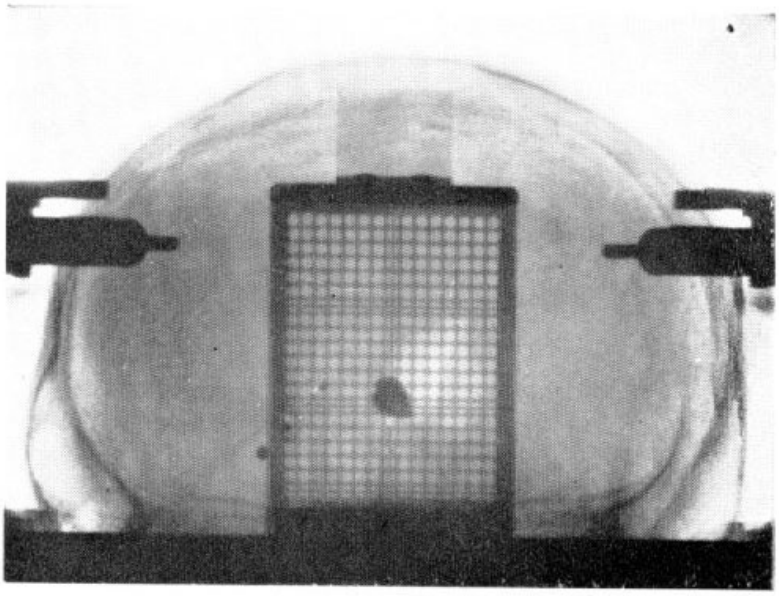


Figure 1 b

Fig. 1 — a et b: 2 téléradiographies de face prises au cours de la même intervention. Un décalage de la visée d'environ 8 degrés, objectivé par la non superposition des trous de la double grille, a déplacé l'image du 3ème ventricule de 5 mm vers la droite; après correction de l'orthogonalité du faisceau (superposition des trous) on voit qu'en réalité le ventricule est situé sur la ligne médiane de l'appareil.

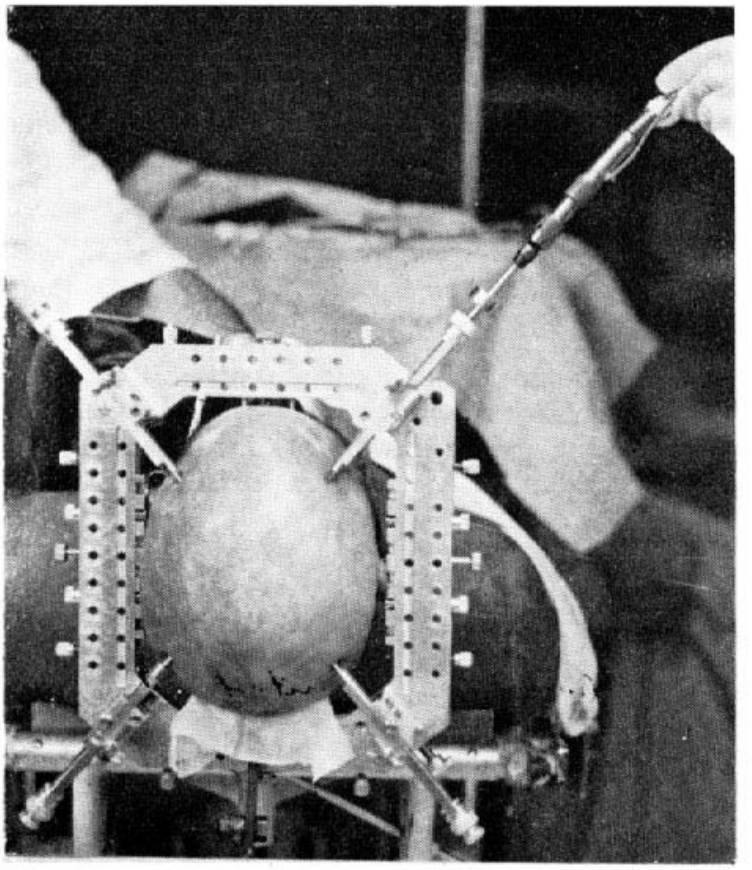


Fig. 2: Mise en place du cadre stéréotaxique: fixation provisoire, forage transcutané d'un orifice osseux définitif.

tantes avec ces structures, des repères intracérébraux visualisés par des examens de contraste sont actuellement adoptés par la plupart des auteurs. Cependant nous devons insister sur le fait que la variabilité considérable et indépendante des différentes coordonnées nécessite des repères et des *lignes de base situés à proximité des structures visées et ayant un rapport organique avec celles-ci* (comme par exemple la ligne CA - CP correspond à la longeur du thalamus).

En plus, comme nous l'avons montré dans notre Atlas d'Anatomie stéréotaxique(2), il est indispensable d'utiliser un *système proportionnel* de coordonnées permettant une localisation individuelle dans chaque cas particulier. Les résultats des mesures récemment publiés par *Mundinger et Pottboff*(3) confirment également ce point de vue. Sans utiliser un tel système de références anatomiques intracérébrales, proches et proportionnelles, il nous parait impossible de localiser avec précision satisfaisante les lésions pratiquées; à plus forte raison deviennent aléatoires les conclusions tirées d'une telle expérience.

2. *Repérage et contrôle radiologiques.*

La transposition des relations spatiales définies lors des études anatomiques s'effectue par l'intermédiaire de procédés radiologiques: nous voulons insister sur l'importance capitale de *l'orthogonalité des projections,* sans laquelle la distorsion de l'image fausse toute localisation. Le système de téleradiographie adopté par nous (distance foyer-objet 4,5 m., la plaque radiologique étant fixé sur le cadre stéréotaxique) diminue déjà au minimum les erreurs dues à l'agrandissement, puisque les rayons X sont pratiquement parallèles. Mais même dans ces conditions favorables, il est indispensable d'assurer et de continuellement contrôler au cours de l'intervention le centrage du rayon central sur les structures visées et son orthogonalité par rapport au cadre stéréotaxique. Un décalage de 8 degrés dans la direction du faisceau des rayons X a déplacé l'image du 3ème ventricule de 5 mm. dans le sens médio-latéral sur les clichés (fig. 1 a et b).

La téléradiographie donne des images pratiquement non agrandies, en dimensions

réelles, ce qui permet *la superposition directe* des images anatomiques et par cela l'utilisation de coordonnées non transformées. A notre avis, ceci représente, —même pour l'introduction d'une seule aiguille—, l'avantage considérable d'éliminer la possibilité d'erreurs de calcul.

Pour la visualisation directe des détails du contour du 3ème ventricule nous utilisons le *lipiodol*, éliminant ainsi les difficultés rencontrées parfois lors de l'interprétation des images aériques.

L'emploi *de doubles grilles identiques*, pour le repérage comme pour l'introduction des aiguilles est une garantie supplémentaire de précision: d'une part la superposition sur les clichés des deux faces de la double grille contrôle directement les conditions radiologiques définies ci-dessus, d'autre part la superposition directe des trous de la grille à travers lesquels on introduira les trocarts et des lignes de référence, élimine les possibles erreurs de la mise en place.

Dans le même ordre d'idées, la *radioopacité des grains d'yttrium* permet un contrôle direct et aisé de la localisation des lésions pratiquées (fig. 9 a et b).

3. *Délimitation objective de la destruction*

Pour pouvoir tirer des conclusions valables de l'expérience chirurgicale il est indispensable de connaître les dimensions et la forme exacte des lésions; or nombre des procédés utilisés couramment, —injection de liquides tel que l'alcool, ou coagulation à haute fréquènce— est caractérisé par l'imprévisibilité des paramètres de la nécrose. En plus, l'emploi de tels procédés implique un certain risque: hémorragies et hémiplégies secondaires dûes à la diffusion des liquides ou à l'irrégularité des coagulations. Ces faits ont incité les auteurs à perfectionner les procédés de destruction. Après avoir utilisé l'électrocoagulation, puis des grains d'or radioactif, nous avons adopté depuis de deux ans comme agent de destruction localisée *l'yttrium 90*, isotope émetteur bêta pur. L'expérience clinique de plus de 250 interventions a parfaitement confirmé les résultats de l'expérimentation animale faite par *Boyesen et Campbell*(4) et par l'un de nous(5).

La nécrose crée par ce corps radioactif s'étend de 3-4 mm. autour de la source; elle est parfaitement limitée, "à l'emportepiéce". Ainsi par exemple un cylindre d'yttrium 90 de 1,13 mm. de diamètre et d'une longueur de 5 mm. ayant une activité de 0.3 à 1 mc. détruit un volume de 0,3 - 0,4 cc. En plus, la surface des grains étant légèrement poreuse, la source conserve son emplacement

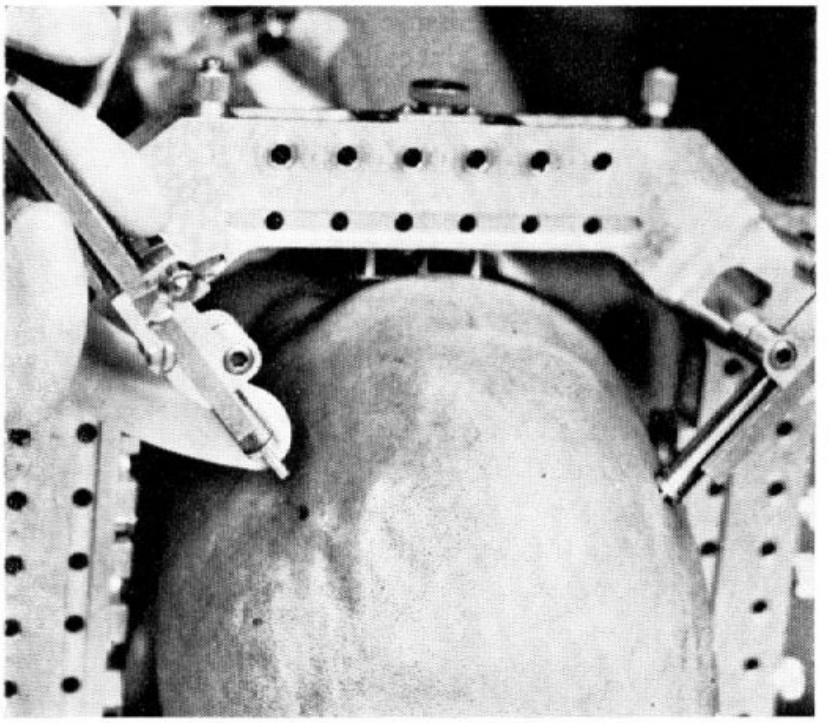


Fig. 3:fixation définitive par pointes mousses.

original, différant en cela des grains ou "seeds" métalliques qui peu à peu se déplacent dans le cerveau. Ainsi la forme et les dimensions des lésions thérapeutiques sont parfaitement définies d'avance ce qui constitue à notre avis un critère également indispensable à toute interprétation ultérieure des résultats. Des lésions d'un volume plus grand mais mal définies peuvent souvent donner des résultats cliniques satisfaisants puisqu'elles atteignent un grand nombre de structures intéressées; mais il serait évidemment difficile d'attribuer una valeur localisatrice très grande à ces techniques peu précises.

Siège de la lésion

Le siège optimun pour obtenir une amélioration de la symptomatologie parkinsonienne est encore matière à discussion. Notre expérience porte sur des syndromes parkinsoniens en général avancés (le sujet ayant le plus souvent dépassé la cinquantaine), à symptomatologie bilatérale à prédominance gauche ou droite chez lesquels sont associés le tremblement, l'hypertonie et l'akinésie, l'un des symptômes étant prédominant.

Depuis 1950, nous avons opéré 150 malades de ce type chez lesquels nous avons effectué divers sortes de lésions thérapeutiques en des points différents des noyaux gris œntraux. Les lésions ont été pratiquées en général au moyen d'agents radioactifs.

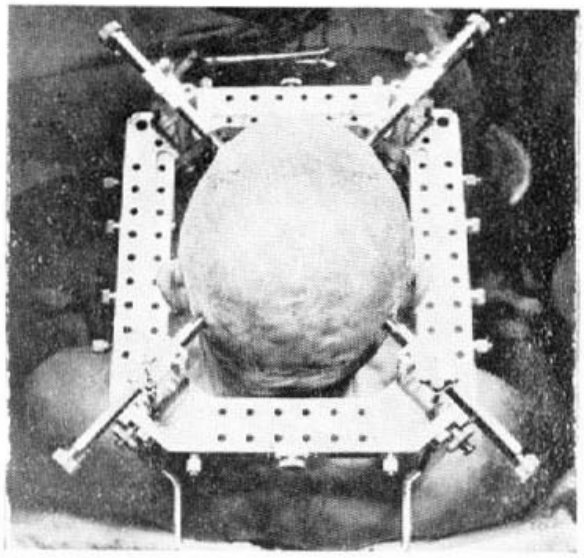


Fig. 4: cadre stéréotaxique en place.

Nous prouvons résumer cette expérience qui nous a engagés, en tenant compte de la situation des produits radioactifs et des résultats thérapeutiques, à *déplacer de plus en plus en arrière les lésions thérapeutiques.*

—Les interventions portant sur la tête du *noyau caudé* ne nous ont pas apporté de modifications importantes du syndrome parkinsonien. Il en a été de même des interventions faites sur la moitié antérieure du *putamen.*

—Les interventions portant sur la portion interne du *pallidum* et de l'*anse lenticulaire* (10 à 15 mm. de la ligne médiane, allant de la commissure antérieure jusqu'à 5 mm. en arrière de celle-ci, et du niveau de la

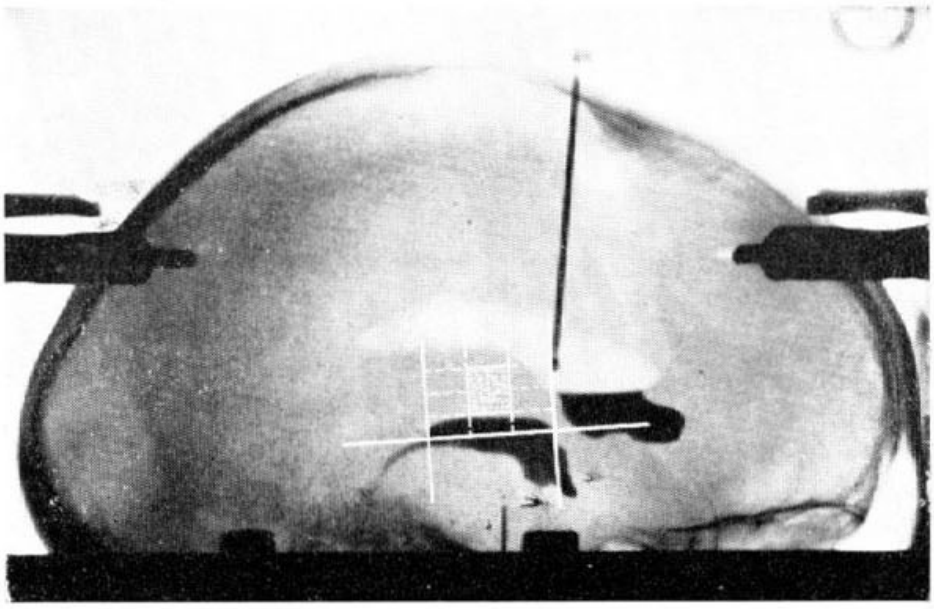


Fig. 5: Objectivation de la ligne de base bicommissurale, avec l'aire de repérage du NVL (téléradiographie de profil).

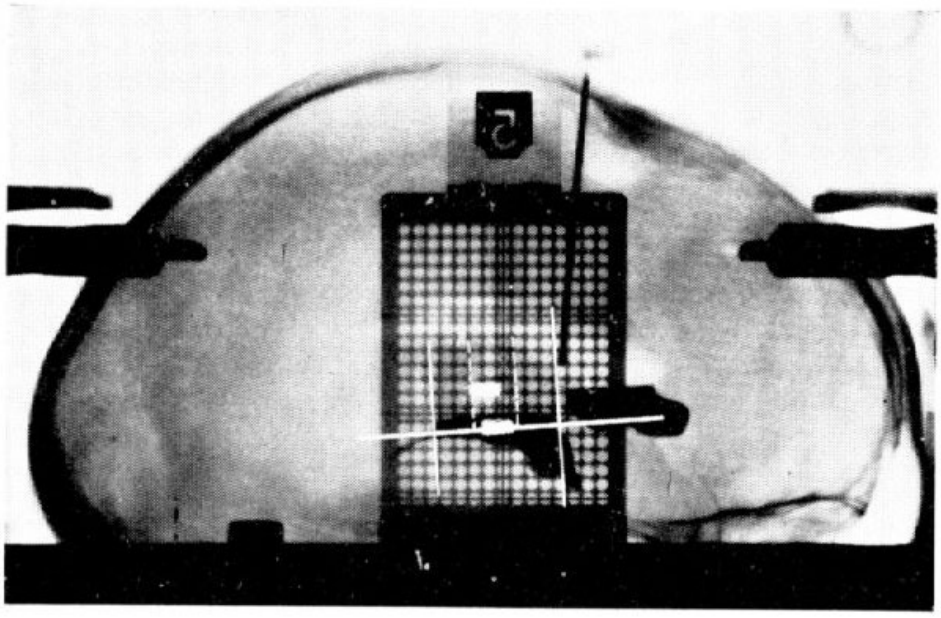


Fig. 6: Définition de l'emplacement des lésions par rapport à l'image de la fig. 5.

ligne bicommissurale également jusqu'à 5 mm. au-dessous) nous ont apporté des résultats médiocres en ce qui concerne l'hypertonie, le tremblement et l'akinésie. La proximité de l'aire hypothalamique latérale n'a pas été sans inconvénient.

—Les destructions effectuées dans le pallidum (à 15 mm. de la ligne médiane, sur le plan de la ligne de base CA - CP à partir de la commissure antérieure et sur une longueur variable allant de la commissure à 5 mm. en arrière) ont donné des résultats assez bons sur la rigidité, moindres sur le tremblement.

A 17 mm. de la ligne médiane ce dernier symptôme est indiscutablement mieux influencé quand la lésion pallidale est plus postérieure et déborde sur la portion motrice de la capsule interne. Cette observation nous avait fait alors penser qu'il était nécessaire d'entrainer un léger déficit pyramidal pour obtenir la suppression du tremblement. Cependant cette façon de procéder n'a pas été sans inconvénient en particulier chez les malades artérioscléreux.

—Les meilleurs résultats, aussi bien en ce qui concerne le tremblement, l'hypertonie et l'akinésie, ont été obtenus *sans déficit pyramidal* à 20 mm. de la ligne médiane, au niveau de la ligne de base et juste en avant de la partie motrice de la capsule interne. Cette région correspond à un niveau où des faisceauxefférents dorsaux du pallidum, dont les fibres à majorité descendante sont orientées horizontalement, traversent le bras postérieur de la capsule interne.

Ainsi il nous est apparu que les lésions effectuées sur le globus pallidus devaient être situées beaucoup plus en arrière qu'il n'était classique de le faire.

Le siège optimum se trouve proche de la portion motrice du bras postérieur de la capsule interne, qui s'est avérée également beaucoup plus postérieure qu'on ne le supposait.

—Les lésions thalamiques dans le NVL entraînent indiscutablement une amélioration importante du tremblement. Elles n' ont pas toujours été suivies d'une modification satisfaisante du syndrome parkinsonien dans sa totalité. Il nous est apparu que les lésions portant sur les 3/4 postérieurs de l'aire de repérage du NVL sont les plus efficaces. Il importe de situer cette lésion assez haut dans le noyau car à la partie basse du NVL la lésion risque d'atteindre les radiations du noyau rouge et peut se compliquer d'un syndrôme cérébelleux transitoire mais très gênant.

Tenant compte des faits précédents qui mettent en valeur les résultats obtenus au cours des destructions de la partie postérieure du GPl et des 3/4 postérieures du NVL du thalamus, nous avons pensé qu'il était possible, en réduisant le volume de chacune des lésions, de pratiquer au cours d'une même intervention une *destruction*

bi-focale thalamique et pallidale. Ainsi les destructions portant sur des systèmes neuronaux fonctionnels un peu différents se complètent mutuellement en agissant à la fois sur le versant des efférences corticales et sur des efférences pallidales orientées vers le tronc cérébral.

Dans les interventions bilatérales que nous ne pratiquons que chez les sujets jeunes présentant un système circulatoire en bon état, la lésion controlatérale est effectuée dans l'une ou l'autre structure, 6 mois après la premiére intervention.

Technique opératoire

Nous n'utilisons pas un appareil spécial pour cette chirurgie du parkinson mais notre cadre stéréotaxique standard qui permet les interventions les plus complexes avec de multiples électrodes (comme dans la chirurgie de l'épilepsie) mais aussi des interventions simplifiées et rapides comme celles que nous allons décrire.

L'intervention est réalisée en un seul temps et dure 1 heure à 1 heure 30.

L'anesthésie générale réclamée actuellement par la plupart des malades est très souvent réalisée. Elle se fait avec intubation endotrachéale avec respiration en circuit ouvert d'un mélange de protoxyde d'azote et d'oxygène. L'anesthésie est réalisée par l'association d'un narcoleptique (20-28 MD) avec un analgésique (R 875) avec adjonction si nécessaire d'un stéroïde analgésique (Viadril).

L'anesthésie générale prive le chirurgien de l'appréciation de l'action immédiate de la destruction. Il faut d'ailleurs souligner que la modification de la symptomatologie immédiatement après la coagulation ne peut être considérée comme un test absolu de l'acte opératoire. Les interventions itératives faites chez des malades éveillés au cours desquelles la coagulation est pratiquée jusqu'à la disparition des symptômes le prouve. Il en est de même dans les interventions pour la douleur dans lesquelles la suppression du phénomène algique en cours de l'intervention n'implique pas que la destruction chirurgicale est suffisante. C'est pour-

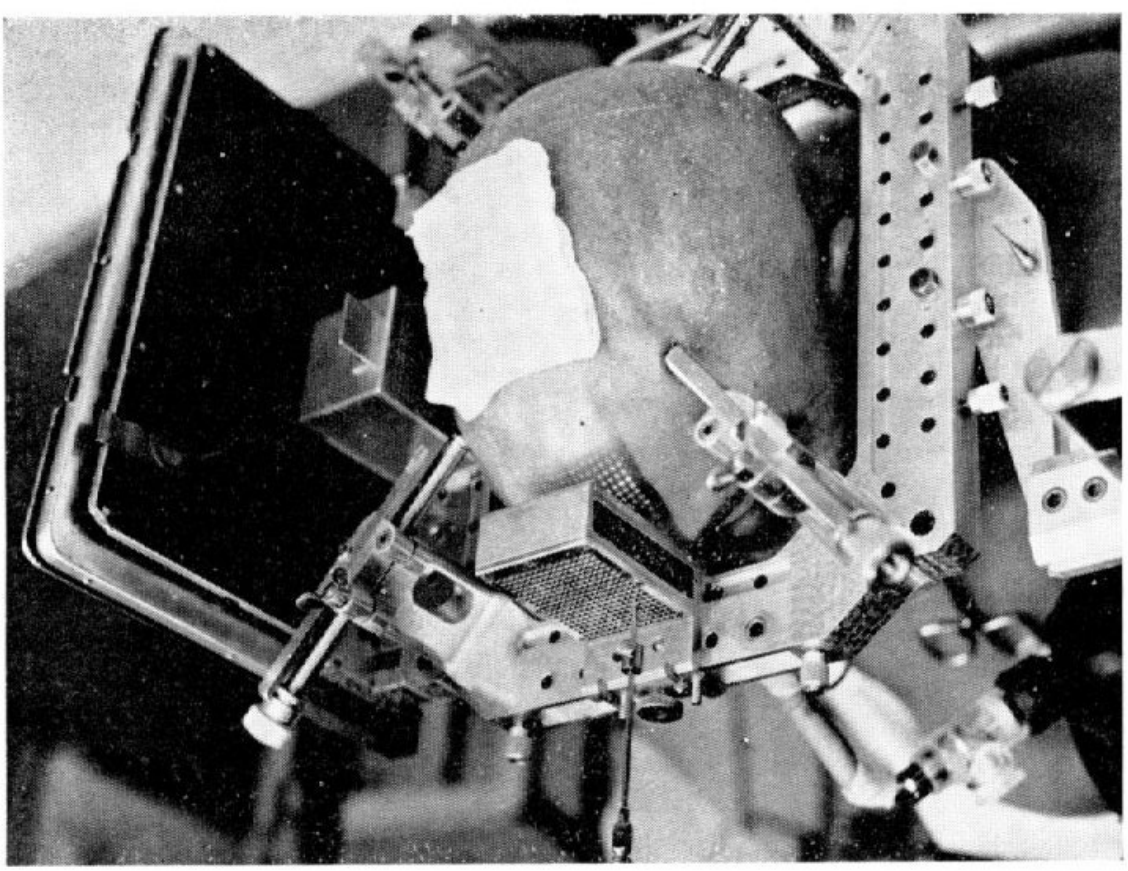


Fig. 7: Double grille de repérage en aluminium, à droite, en acier cépenté pour forage des trous, en haut.

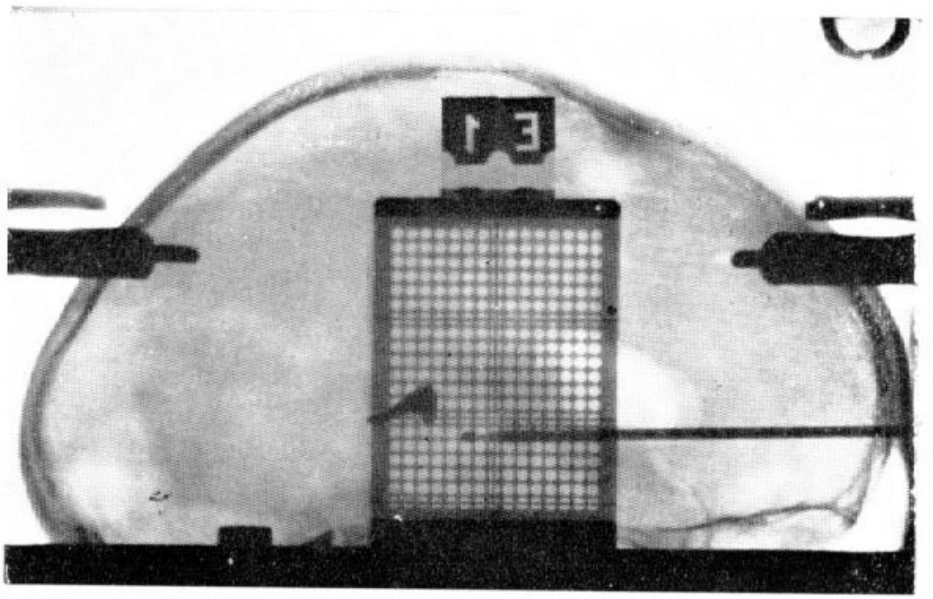


Fig. 8: Position de l'électrode de stimulation lors de la première réponse motrice (à 21 mm de la ligne médiane). Téléradiographie de profil.

quoi nous préférons pratiquer une anesthésie générale qui rend l'intervention plus confortable pour le malade tout en permettant des contrôles radiologiques plus méticuleux. De plus, elle ne gêne pas la stimulation des fibres motrices de la capsule interne qui est effectuée au cours de chaque intervention pour délimiter le pallidum des voies motrices.

Nous pratiquons des explorations neurophysiologiques chez des malades jeunes pour lesquels la durée de l'intervention n'a pas d'incovénient. Dans ce cas, la première partie de l'intervention (mise en place de l'appareil stéréotaxique, repérage, introduction des électrodes) se fait sous intubation avec l'association analgésique neuroleptique sans stéroïde. Cette anesthésie fugace permet la récupération rapide de l'état vigile dès que les électrodes sont en place.

La position opératoire prend chez les parkinsoniens, surtout âgés, une grande importance. Ces sujets souvent fragiles supportent mal une station assise prolongée, source de collapsus grave, et la plupart des neuro-chirurgiens qui l'utilisent ont du sérier les temps opératoires ou s'adresser à des méthodes palliatives pour maintenir un taux tensionnel suffisant. En outre, cette position facilite le décollement du cerveau.

La technique utilisée permet de conduire la majeure partie de l'intervention en decubitus dorsal. La position assise n'est utilisée que temporairement pour le seul temps de repérage lipiodolé, dont la durée n'excède en général pas une dizaine de minutes.

a) *Mise en place du cadre stéréotaxique.*

Elle est facile sur le malade en decubitus dorsal, la tête posée en dehors de la table sur un appui-tête de ventriculographie ou tout autre support analogue.

Le cadre est disposé verticalement reposant par sa pièce d'appui antérieur échancrée sur l'arête nasale juste au-dessous du nasion. En agissant sur la vis qui permet d'avancer ou de reculer cette pièce d'appui nasal il est aisé d'amener les petites olives métalliques qui terminent les tiges de fixation auriculaire en regard des conduits auditifs externes. Les deux tiges filetées sont vissées et enfoncées symétriquement. La pièce d'appui occipital est amenée à son tour au contact de la voûte au voisinage de la protubérance occipitale externe (fig. 2).

Cette fixation provisoire est complétée par quatre tiges mousses amovibles orientées selon l'axe des supports situés aux angles du cadre. Ces tiges sont fortement pressées contre la voûte.

Cet ensemble de points d'appui cutanés maintient rigoureusement le cadre en place pendant le forage des orifices osseux définitifs.

A ce stade il est bon de vérifier que la ligne médiosagittale du crâne correspond sensiblement à l'axe médian antéro-postérieur du cadre. C'est pratiquement toujours le cas, sinon il est facile de modifier la position du cadre en agissant sur les différentes fixations.

Fixation définitive

Une fixation solide à l'os est absolument indispensable. Le dispositif de fixation doit aussi permettre la reposition *du cadre dans une situation identique lors des réinterventions éventuelles.* Nous utilisons quatre points de fixation osseuse opposés en diagonale. Des courtes pointes mousses sont introduites après trépanation transcutanés et sont enfoncées à une profondeur repérée par une graduation solidaire des 4 supports. Le mode opératoire est simple. Une des tiges de fixation provisoire est retirée, elle est remplacée par un foret de faible diamètre: 3 mm., coulissant dans la lumière du tube-guide du support (fig. 2). La rotation rapide du foret facilite sa pénétration à travers la peau et dans la voûte. La profondeur de pénétration est limitée par une butée règlable. Il importe peu en pratique que la table interne soit ou non respectée.

Le foret est retiré, remplacé par une pointe mousse qui est enfoncée dans l'os selon l'axe de la trépanation en vissant le tube guide précité (fig. 3).

Les trois autres pointes sont ainsi introduites successivement. Ce mode de fixation par des axes en diagonale est absolument rigide et ne permet aucun déplacement quels que soient les mouvements des malades, ce qui a une importance capitale lors-

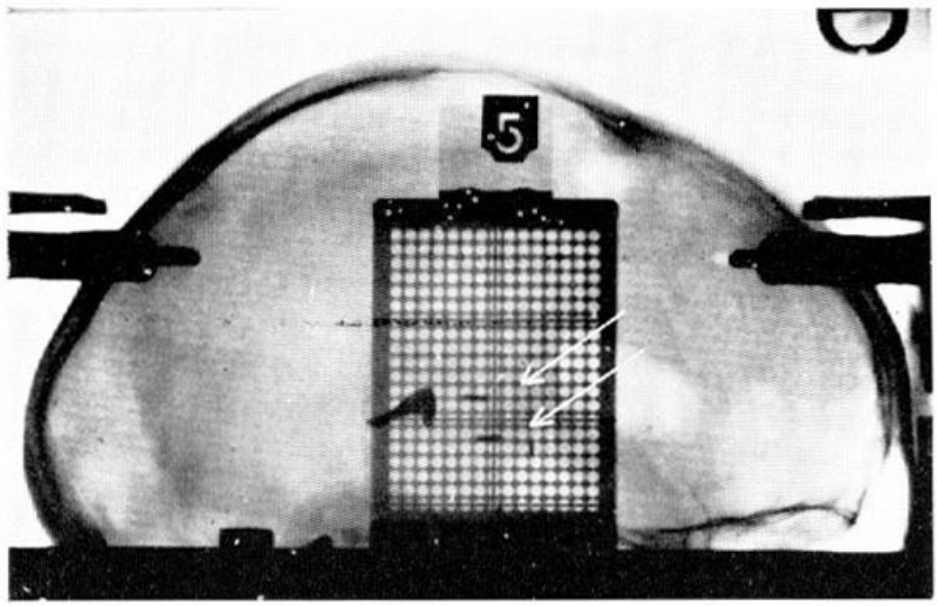


Fig. 9: —a: Les grains d'Y 90 en place (lésion bi-focale: GPl et NVL Th). Téléradiographie de profil.

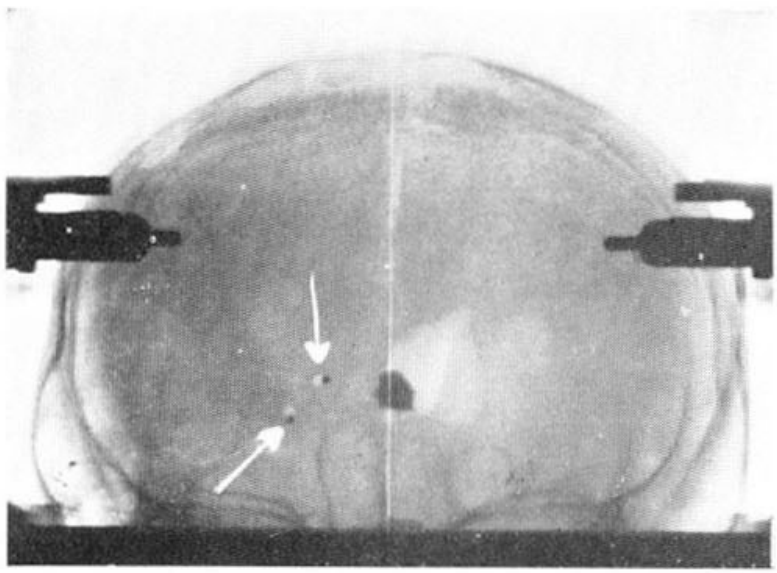


Fig. 9 — b: Téléradiographie de face.

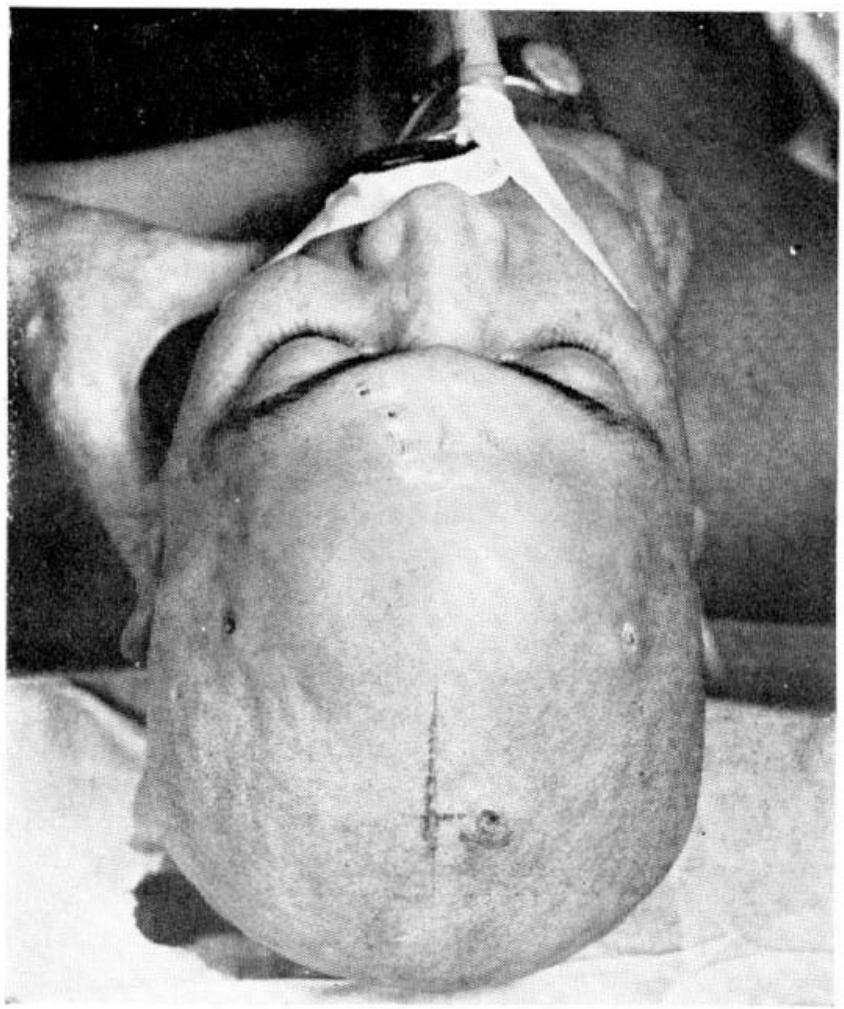


Fig. 10: Tête du malade après l'ablation du cadre.

que plusieurs électrodes sont introduites dans le cerveau. Il se traduit en définitive par des plaies cutanées minimes ne nécessitant pas de points de sutures et laissant des cicatrices en pratique invisibles (fig. 10).

Repérage lipiodolé

La ponction de la corne frontale droite est pratiquée après trépanation transcutanée au moyen d'une petite fraise de 3 mm. de diamètre. La dure-mère est ouverte avec une tige coagulante fine, l'orifice est agrandi et le cortex coagulé avec une sonde mousse d'un calibre de 2 mm.

Il arrive, rarement, qu'une hémorragie veineuse notable traduise l'ouverture d'une granulation de Pacchioni ou d'une veine corticale. L'hémostase a toujours pu être obtenue soit par des coagulations répétées, soit par obturation temporaire de l'orifice osseux. Il n'a encore jamais été nécessaire de réaliser l'hémostase sous contrôle de la vue.

Le plus souvent le liquide s'écoule spontanément. L'absence d'écoulement est possible bien que la ponction soit correcte lorsque la pression est faible et l'aiguille à la partie très antérieure de la corne frontale. Une aspiration douce à la seringue confirmera le siège intraventriculaire de l'aiguille. Il est toujours prudent de contrôler par un cliché la situation de l'aiguille après injection d'un à deux cc. d'air afin d'éliminer l'éventualité d'une ponction des espaces sous-arachnoïdiens. Une butée mobile est serrée sur l'aiguille au contact de la peau. Elle préviendra toute fausse manoeuvre et toute hésitation lors de l'injection du lipiodol.

Le malade est alors assis, la tête placée de telle sorte que le cadre stéréotaxique soit horizontal. Dans cette position, qui facilite l'examen radiologique, le lipiodol injecté dans la corne frontale (1,5 cc. environ) atteint le trou de Monro, pénètre dans le 3ème ventricule qu'il emplit transitoirement jus-

qu'à un niveau supérieur à l'orifice de l'aqueduc. Dans la grande majorité des cas les commissures antérieure et postérieure sont parfaitement visualisées sur la même radiographie (fig. 5). Parfois la commissure antérieure seule est visible, la quantité de lipiodol est insuffisante pour atteindre l'aqueduc parce que la corne frontale est dilatée et retient une certaine quantité de contraste. Dans cette éventualité, il nous a paru préférable d'injecter à nouveau 1 à 1,5 cc. de lipiodol, plutôt que de basculer la tête en arrière. Cette manoeuvre peut en effet rendre difficile le maintien en bonne place de la totalité du lipiodol pendant un délai suffisant.

Dès que l'injection de contraste est terminée nous prenons une série de trois téléradiographies de profil, la dernière, après avoir placé sur le cadre une double grille dont l'image superimposée à l'image ventriculaire servira à repérer la situation des structures visées par rapport à l'appareil stéréotaxique. Les contrôles ultérieurs de la mise en place des trocarts ou des grains radioactifs seront faits sur des films de profil, par rapport à l'image de la même grille maintenue en place sur le cadre. Cet artifice de repérage au moyen d'une grille constitue un caractère original de cette technique et rend inutile le maintien prolongé du lipiodol dans le système ventriculaire. Des téléradiographies de face avec et sans grille, sont pratiquées ensuite. A ce moment le lipiodol n'occupe plus que la partie déclive antérieure du 3ème ventricule mais cette image est suffisante pour définir la ligne médiane et fixer sa situation par rapport à la grille frontale.

Dès que l'examen radiologique est terminé, le malade est à nouveau allongé et restera en decubitus pour les temps suivants de l'intervention. Dans cette position une radiographie de face (Fig. 1 b) pourra visualiser le recessus supra-pinéal seul injecté et confirmer la position correcte du cadre en montant les portions antérieure et postérieure du 3ème ventricule alignées vers l'axe médian de la grille frontale ou parallèlement à cet axe en cas de léger décalage latéral global qui d'ailleurs n'affecte en rien la précision de l'intervention.

C — *Utilisation des données radiologiques*

Les clichés sont l'object d'un développement rapide avec séchage après bain d'alcool. De la sorte, il est possible rapidement de dessiner sur les clichés les lignes de base permettant d'objectiver les points à atteindre.

a) *Objectivation des lignes de base* (fig. 5 et 1 b). On voit sur la fig. 5 mettant en valeur l'injection du 3ème ventricule par le lipiodol, la ligne de base proportionnelle CA - CP prenant point d'appui sur les commissures antérieure et postérieure. A partir de cette ligne de base pourront être établies les aires de repérage des noyaux gris centraux.

On voit sur la fig. 1 b les rapports de la ligne médiane du cerveau avec celle de

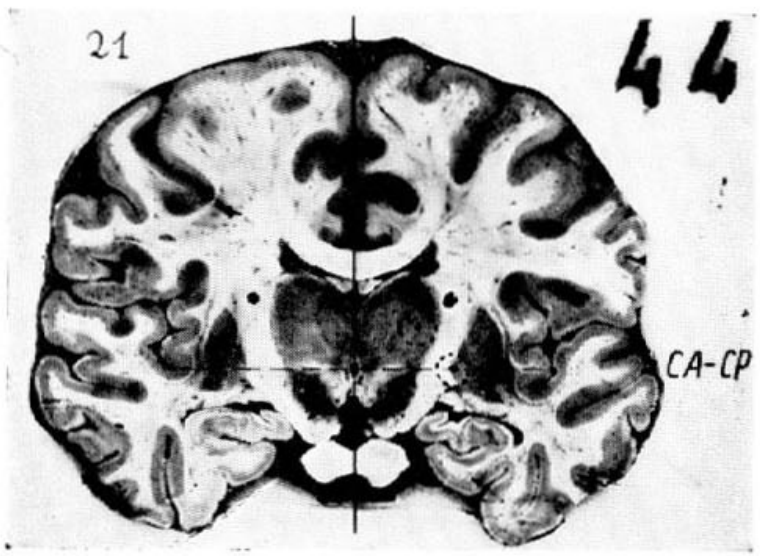
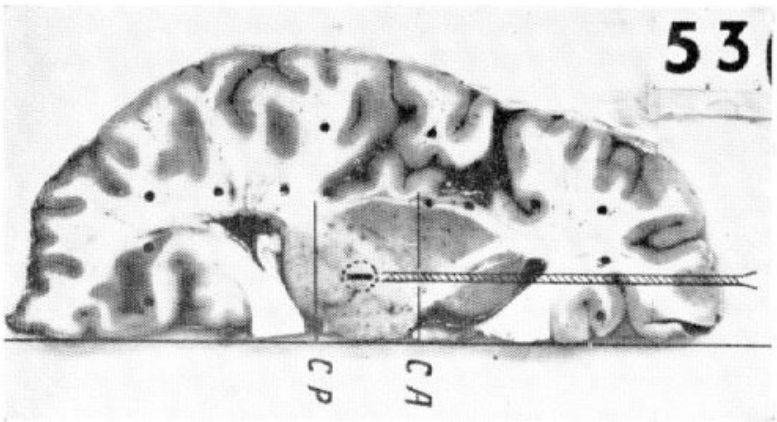
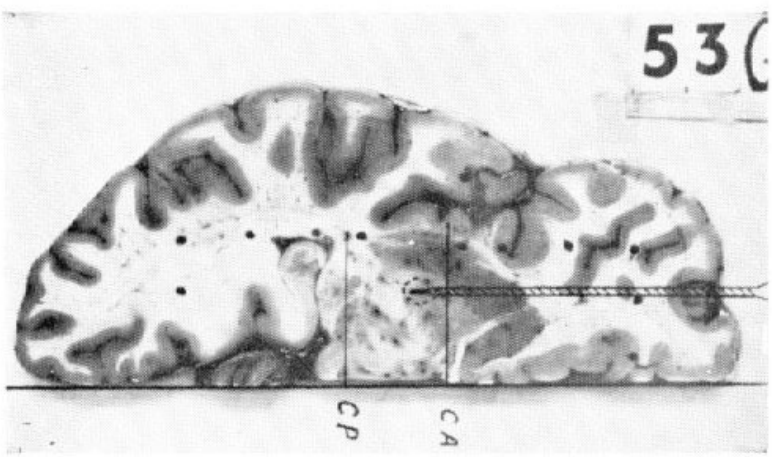


Fig. 11: Coupe vertico-frontale au niveau des lésions (en pointillé).



a: NVL Th



b: GP1

Fig. 12 — a et b: Coupes horizontales au niveau des lésions (en pointillé)

l'appareillage. Ce qui permet, s'il y a lieu, de faire la correction nécessaire.

b) *Objectivation du point à atteindre* (fig. 6). Nous pratiquons, comme nous l'avons dit précédemment, simultanément du même côté deux lésions: l'une dans le globus pallidus, l'autre dans le thalamus au niveau du noyau ventral latéral.

1. *Lésion pallidale.* — Elle est effectuée à une distance de 20 à 21 mm. de la ligne médiane, sur le plan de la ligne CA - CP. Dans le sens antéro-postérieur, la lésion doit être pratiquée juste en avant de la première réponse motrice du bras postérieur de la capsule interne. Ces réponses se situent dans le tiers moyen de la ligne de base CA - CP. Il est préférable, comme nous le verrons plus loin, de pratiquer à ce niveau une excitation de la capsule interne pour préciser les limites postérieures du globus pallidus et éviter ainsi les déficits pyramidaux consécutifs à la destruction (fig. 8).

2. *Lésion thalamique* (fig. 6). — Le centre de la lésion est situé à 14 à 15 mm. de la ligne médiane, 8 à 9 mm. au-dessus de la ligne de base et dans la partie postérieure de l'aire de repérage du noyau ventral lateral. Les lésions pratiquées à ce niveau nous ont apporté des résultats beaucoup plus satisfaisants que celles pratiquées au niveau de la partie antérieure du même noyau.

D — Destruction des structures

Pour l'introduction des sondes permettant la mise en place des grains d'yttrium, nous utilisons la voie la plus simple et la plus précise qui est la voie horizontale frontale.

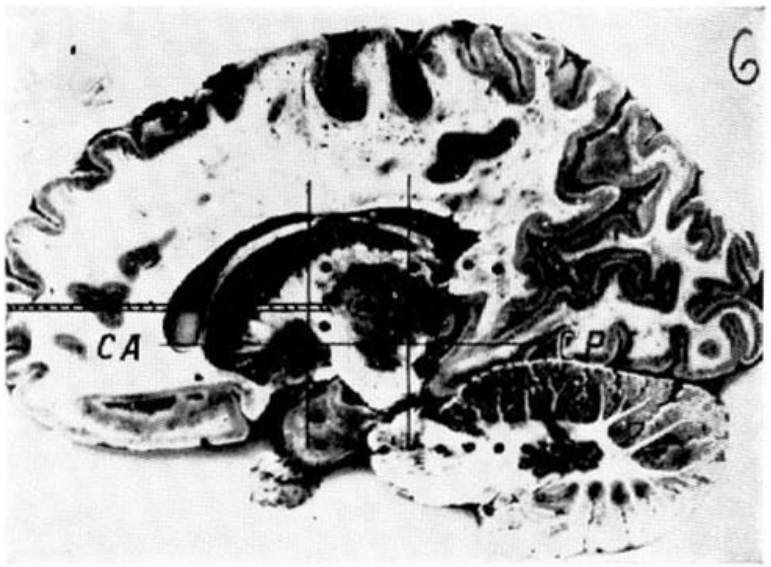
En effect, connaissant les rapports de la lésion à pratiquer avec les orifices de la double grille latérale (fig. 5 et 6) il est facile d'introduire 1 ou plusieurs trocarts par voie frontale dirigés par les orifices d'une double-grille identique (fig. 8). Il suffira de choisir l'orifice correspondant si-

tué à la distance désirée de la médiane (15 et 20 mm.). Un artifice permet de déplacer cette double-grille d'un demi trou en haut ou latéralement de façon à pouvoir atteindre un point intermédiaire entre les orifices des grilles de repérage.

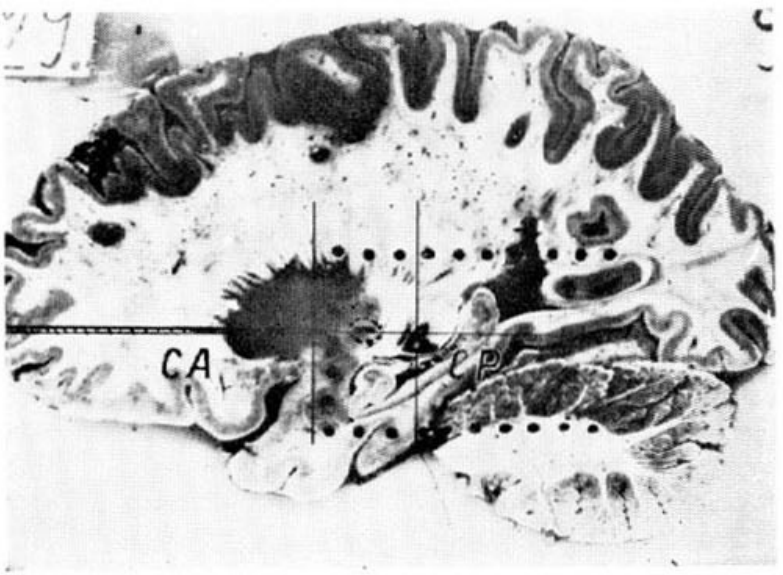
La grille utilisée (fig. 7) est une double grille spéciale en acier cémenté résistant à la rotation rapide à travers ses orifices d'une fraise en acier. Ceci permet une trépanation transcutanée au moyen d'un foret d'un calibre de 2,5 mm. coulissant dans les orifices choisis d'après le repérage. Une butée mobile est fixée de manière à limiter la pénétration trop profonde du foret.

Il est préférable pour éviter de déchirer la dure-mère de rester d'abord en deçà de la longueur nécessaire à une trépanation de la table interne et de la compléter par petites touches. La dure-mère est ouverte au moyen d'une tige coagulante qui coagule également le cortex sur une profondeur d' 1/2 à 1 cm. Nous n'avons jamais observé d'hématomes extra ou sous-duraux.

c) Les sondes pour stimulation ou les trocarts à yttrium du même diamètre, sont alors introduits à travers la grille puis sans difficulté dans l'axe des trépanations et des cheminées cérébrales préparées. Ils sont enfoncées lentement en imprimant de petits



a: NVL Th



b: GPI

Fig. 13 a et b: Coupes sagittales au niveau des lésions (en pointillé)

mouvements de rotation sur l'axe afin d'éviter l'étirement d'un vaisseau. Le sinus frontal ne représente pas un obstacle à cette voie d'abord et nous l'avons fréquement traversé sans précaution spéciale et sans aucune complication infectieuse. Seuls l'existence d'une sinusite latente ou d'un voile dense sur les radiographies peropératoires pourraient contreindiquer cette voie d'abord directe et faire préférer un abord antérieur oblique et l'utilisation d'un angulateur. Cette éventualité n'a pas été rencontrée chez nos malades.

Le trocart à yttrium est enfoncé dans le thalamus jusqu'à la partie postérieure de l'aire de repérage. Puis il est retiré d'une longueur égale à celle de la particule d'yttrium qui sera pousée à travers le trocart.

En ce qui concerne la destruction pallidale pour laquelle une stimulation de la capsule interne est nécessaire, une électrode est introduite jusqu'au 1/3 moyen de la ligne CA - CP. Une première stimulation est pratiquée en ce point, si elle n'a en aucun effect l'électrode est enfoncée millimètre par millimètre pour obtenir une réponse motrice qui porte sur l'hémiface controlatéral parfois associée à une réponse au niveau de la main. Les contractions sont très parcellaires, mettant en jeu quelques muscles, comme langue, zygomatique, houppe du menton, orbiculaire des lévres, le peaucier, à la main un interosseux, l'extenseur de l'index, l'adducteur et l'opposant du pouce. Ces réponses sont rigoreusement controlatérales au membre supérieur, souvent bilatérales au niveau de l'orbiculaire des paupières ou du frontal. La première réponse motrice obtenue signifie que le pallidum est dépassé et que la pointe se trouve au contact de la capsule interne motrice.

La position de la sonde est soigneusement repérée (fig. 8), le grain d'yttrium est placé de sorte que son pôle postérieur reste un peu en avant (1 à 2 mm.) des fibres motrices. La lésion siège donc avec certitude en avant des voies pyramidales.

Des clichés de contrôle (fig. 9 a et b) permettent de déterminer le siège réel de la destruction par comparaison avec les clichés de repérage.

Il nous est ainsi possible d'établir sur des coupes anatomiques la situation et la dimension exactes des destructions pratiquées.

Les coupes des figures (11 - 12 - 13) sont destinées à mettre en valeur suivant les divers plans de l'espace la situation et la dimension de ces lésions.

1º) *Coupe vertico-frontale* (lésion pallidale et thalamique) passant par le plan moyen de la destruction (fig. 11).

On voit que les lésions sont situées de part et d'autre de la capsule interne à des niveaux différents. On voit également que la lésion pallidale déborde sur le bras postérieur de la capsule interne. A ce niveau seule une partie des fibres concernant la face peut être lésée, ce qui provoque une légère parésie faciale. Par contre la lésion n'entraîne pas de déficit moteur du membre supérieur, les fibres motrices concernant le bras s'étalant juste en arrière de la coupe présentée (cf. coupe sagittale passant à 20 mm. de la ligne médiane: fig. 15).

2º) *Coupes horizontales* (lésion pallidale) (fig. 12 b).

La coupe passe par les commissures antérieure et postérieure suivant la ligne de base CA - CP. Elle indique la position du grain d'yttrium à 21 mm. de la ligne médiane situé juste en avant de la partie motrice de la capsule interne. Le traject de l'électrode qui passe par un plan connu permet de faire l'étude systématique des structures traversées (face orbitaire du lobe frontal —partie antérieure du putamen— partie postérieure du globus pallidus).

3º) *Coupes horizontales* (lésion thalamique, fig. 12 a) passant à 8 mm. au-dessus de la ligne de base CA - CP. La sonde horizontale passe à 15 mm. de la ligne médiane à travers la partie haute de la face orbitaire du lobe frontal, la tête du noyau caudé, le bras antérieur de la capsule interne, le bras postérieur (non moteur) et le noyau ventral latéral thalamique.

4º) *Coupes sagittales* (lésion pallidale, fig. 13 b) passant à 20 mm. de la ligne médiane. On voit le traject de l'électrode destinée à stimuler la capsule interne. Le grain d'yttrium est placé à 2 mm. en avant des réponses motrices concernant la face.

5º) *Coupes sagittales* (lésion thalamique, fig. 13 a) passant à 15 mm. de la ligne

médiane. On voit le trocart qui n'a pas rencontré dans son parcours de fibres motrices. Le grain d'yttrium est placé dans les 2/3 postérieurs de l'aire de repérage du NVL TH à 8 mm. au-dessus de la ligne de base CA - CP.

RESUMÉ

1) Les auteurs exposent brièvement les conditions méthodologiques de stéréotaxie qu'ils estiment indispensables dans la recherche des corrélations anatomo-cliniques concernant le syndrome de Parkinson. Pour pouvoir tirer des conclusions valables de l'expérience stéréotaxique sur la valeur et la signification de lésions pratiquées dans telle ou telle structure intracérébrale, il faut que l'intervention soit entourée de multiples garanties de précision. Les auteurs insistent particulièrement:

a) sur la nécessité d'utiliser un système de références anatomiques proportionnelles ayant un rapport organique avec les structures intéressées, à proximité des points visés,

b) sur l'importance d'une très correcte orthogonalité dans les projections radiologiques qui seule peut permettre une transposition valable du système de références au cas particulier,

c) sur la nécessité de pratiquer des lésions de volume et de forme bien définies.

2) L'experience a conduit les auteurs à pratiquer des lésions bifocales, pallido-thalamique, qui donnent incontestablement les meilleurs résultats thérapeutiques.

3) Une brève description de la technique opératoire est illustrée par des images radiologiques peropératoires avec les coupes anatomiques correspondantes démontrant l'emplacement des lésions.

SUMMARY

1) Authors discuss the essential conditions they think indispensable for correct interpretation of the results of stereotactically produced intracerebral destructions and for further research concerning anatomo-clinical correlations in parkinsonism. They emphasize the necessity of great precision in the operating technique, in particular,

a) the importance of a proportional system of anatomic coordinates, the reference-lines being near to and in organic relation with the structures in question;

b) the necessity of continually controlled strict orthogonality in the X-ray projections, condition sine qua non of correct transposition on the individual brain of spatial relations determined by anatomical studies;

c) the importance of making lesions of known form and size.

2) Best therapeutical results were obtained by bifocal, pallido-thalamic destructions, using radioactive yttrium 90 seeds.

3) A brief description of the operating technique is illustrated by peroperative X-ray pictures and corresponding brain-slides showing localization of destructions.

RESUMEN

1. Los autores exponen brevemente las condiciones metodológicas de la estereotaxia que consideran indispensable en las investigaciones para establecer correlaciones anatomoclínicas en el síndrome de Parkinson. Para extraer conclusiones útiles de la experiencia estereotáxica acerca del valor y significado de las lesiones practicadas en tal o cual estructura cerebral es necesario que la intervención esté rodeada de amplias garantías en cuanto a su precisión. Los autores insisten particularmente en:

a) la importancia de un sistema proporcional de coordenadas anatómicas, con líneas de referencia próximas y en relación orgánica con las estructuras en cuestión;

b) la necesidad de una ortogonalidad estricta y controlada continuadamente en las provecciones radiológicas, condición imprescindible para la correcta transposición so-

bre cada caso en particular de las relaciones espaciales determinadas por los estudios anatómicos;

c) sobre la importancia de hacer lesiones de forma y tamaño conocidos.

2. La experiencia ha conducido a los autores a practicar lesiones bifocales, pálido talámicas, que son las que dan sin discusión los mejores resultados terapéuticos.

3. Una descripción breve de la técnica operatoria es ilustrada por imágenes radiológicas peroperatorias con los cortes anatómicos correspondientes que muestran la localización de las lesiones.

ZUSAMMENFASSUNG

1. Es werden die metodologischen Bedingunden der Stereoataxie beschrieben, die unerlaesslich sind bei der Untersuchung der anatomisch-klinischen Beziehungen des Parkinson-syndroms. Um gueltige Schlussfolgerungen zu ziehen aus den stereoataxischen Versuchen ueber den Wert und die Bedeutung der chirurgischen Eingriffe in der intracerebralen Struktur, ist es noetig, dass die Operationstechnik genauen Vorschriften folgt. Die Autoren insistieren vor allem.

a) auf die Notwendigkeit, ein proportionelles System anatomischer Koordinaten zu benuetzen, die in organischer Beziehung stehen zu den in Frage kommenden Strukturen,

b) auf die Wichtigkeit einer ganz genauen Orthogonalitaet in der roentgenologischen Projektion, welche erlaubt, Rueckschluesse von der roentgenologischen Untersuchung auf die individuelle anatomische Struktur zu ziehen,

c) auf die Notwendigkeit, Eingriffe vorzunehmen, deren Form un Lokalisation genau umschrieben sind.

2. Auf grund ihrer Erfahrungen machen die Autoren bifokale Eingriffe, Pallidothalamische Zerstoerung, welche die besten therapeutischen Resultate geben.

3. Eine kurze Beschreibung der Operationstechnik ist illustriert durch waehrend der Operation gemachte Roentgenbilder und durch die entsprechenden anatomischen Schnitte, welche die Lokalisation der operativen Zerstoerung zeigen.

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Personality

Sir RUSSELL BRAIN

"Writing biography is an art like portrait painting" said Andre Marois. The comment of this seasoned writer calls us to reflect on the responsibilities of transmitting a true picture of a personality in a sketch's brief manner.

The most important features must be chosen and those details stressed which are the dominant aspects of a life.

Moreover unlike a portrait which reflects in a given moment all the impact of a personality, a biographical note must describe in the fourth dimension, taking a panoramic view of a life.

To neurologists who are regularly attending Congresses of our specialty Sir Russell Brain is a familiar figure. This silver-haired soft-spoken, self-composed British neurologist, with a kind smile always brightening the gaze of his light eyes, is surrounded by the respect and affection of his colleagues and is one of the leading figures of English neurology.

Son of a lawyer, he originally intented to follow in the footsteps of his father. With this in mind he devoted most of his time to reading classics and history at school. Then the First World War broke out, and in its shattering wake plans were disrupted. Destiny pointed to his life its true route, when he started work in the X Ray Departments of Military Hospitals.

There he found romance and his lifetime career. It was there that he met his wife, who came from a medical family. Her father and grandfather and several relatives were doctors. Her grandfather was Langdon-Down who first described mongolism. Whether or not this had something to do with changing his mind, the truth is that after the war ended the

prospective lawyer returned to Oxford to read Medicine. There many stimulating experiences were waiting for him. Somebody said. "No man or woman was ever left to fight alone the battle of life. All great man were surrounded by friends and enemies". Among our greatest friends are our teachers and young Russell had the best of them. J. B. S. Haldane was his inspiring tutor, and the fascinating realm of Biology was disclosed to his eyes through the masterful guidance of Julian Huxley. To complete the set of outstanding professors, Sherrington was at that time teaching physiology. But it was his physiological tutor Bazet, who influenced him to follow Neurology.

He was also attracted to Psychiatry and at one time he had the intention to become a psychiatrist.

But when he went to the London Hospital, which was the hospital where his wife's father and grandfather had been educated, another valuable contact was made there. There he met Riddoch who earned a well known reputation working with Henry Head during the war. He was the person who persuaded Russell Brain to become a neurologist and who obtained for him the first neurological appointement. This was as house physician at the Maida Vale Hospital, which he held directly after qualifying. Afterwards Riddoch and he worked together at the London Hospital, until he left to devote his attention to the Maida Vale Hospital as Medical Registrar.

In 1925 he was elected assistant physician there, and invited to be a member of the staff of the London City Hospital in 1927.

In 1950 he was elected President of the Royal College of Physicians of London a position which he occupied until 1957. In that lapse of time, fruitful steps were taken in negotiations with the Ministry of Health concerning the launching of the National Health Service. Nowadays he is the current President of the Association of British Neurologists.

Throughout his life Sir Russell Brain maintained a constant awareness about every human endeavor in literature, art, and science.

Himself a writer, who began to enjoy the thrill of creative writing at school, he has devoted many hours of his busy life to works of literature. Besides he has made well known contributions to the field of neurological science through books like "Recent Advances in Neurology" which he wrote jointly with Dr. Eric Strauss, and whose first edition appeared in 1929. In 1933 he published a book on "Diseases of the Nervous System". Another contribution to contemporary neurology recently appeared with a book on "Clinical Neurology". He is Editor of "Brain", the well known British medical journal. Many papers and lectures testify to the keen clinical ability of this neurologist who talks about science like an artist, and scrutinizes art like a scientist.

His best known contributions to neurology have been his description of the carpal tunnel syndrome, his contributions to our knowledge of cervical spondylosis and carcinomatous neuromyopathy and his studies of aphasia. In the field of general medicine he has been interested in thyroid disease and invented the term exophthalmic ophthalmoplegia.

But until we are intimate with his thoughts outside medicine, we really miss the most fascinating side of this interesting personality.

Travel through to the past and here we are in England after dark. A boy is advidly reading "Treasure Island" by candlelight, while the shadows play a mysterious ballet on the walls.

There is something esoteric about the enthusiasm that arises from the idea of looking for hidden treasures. The boy grows up and becomes

a successful neurologist, and the same animated state of spirit is transferred to the higher levels of the intellect. Thus, now aside from his professional interest, he constantly delves into the genius expressed in art, literature, philosophy and the theatre, with the same exploring eagerness with which he pored over Stevenson's tales. But behold, he could never entirely get away from his medical self, for the doctor was peering over his shoulder and he was unconsciously making diagnoses. Here lies over my desk the fruits of his search "Some Reflection on Genius". The cover is inviting, and I open the book and enter into it like Alice did "Through the Looking Glass" to get a close up of Sir Russell Brain on life and the toils of genius.

"Some Reflection on Genius"

There is Jonathan Swift, l'enfant terrible, the intellectual father of Gulliver; with his emotional inmaturity, unable to publicly marry Stella the object of his love (somebody believed they were secretely married). Suffering from a Mennier's Syndrome, the life of this successful writer was one of permanent invalidism, to end almost deaf with his vision seriously impaired, a "Shadow, of a shadow of a shadow..." as he states and Sir Russell Brain quoted in his accurate study of this singular character.

Next we can guess who is the approaching bulky figure. It is Dr. Johnson. This English, phylosopher and amateur scientist, with a prodigious memory, an unfailing deep curiosity for everything that appeals to the human mind, whether be it chemistry, "air balloon" navigation or natural history, has also a morbid personality and Sir Russell Brain, studies all the aspects of his fascinating life, to which he devoted many pages of his book "Some Reflexions on Genius".

Dr. Johnson suffered from compulsory obsession to perform some elaborate ceremonies, and a reconstruction of his life through the testimony of his contemporaries throws light about his pleasures and sorrows.

Sir Russell gives us a medical document including in his book Miss Reynold's narration of Dr. Johnson's behavior.

"He began his antics with his feet and with his hands with the latter as it he were holding the reins of a horse like a jockey at full speed..... I well remember that they (his gestures) were so extraordinary that men, women and children gathered round him laughing.

At last we sat down on some logs of wood by the riverside, and they nearly dispersed; when he pulled out of his pocket Grotius' "De Veritate Religionis", over which he seesawed at such a violent rate as to excite the curiosity of some people at a distance to come and see what was the matter with him".

Amid the interesting disclosures of Dr. Johnson's abilities these touches of shadow gave a dramatic aura to these studies on genius and remind us that those portraits by Rembrandt in which light emerges as a result of the shadows emphasizing the subject's most striking features.

Thus memory, the basic tool of his encyclopedic knowledge, was also a torture instrument.

Sir Russell quotes Mrs. Thrale as saying: "Reasonable with regard to others, he had formed vain hopes of performing impossibilities himself; and finding his good works ever below his desires and intent, filled his imagination with fears that he should never obtain forgiveness for omissions of duty and criminal waste of time. His sense of guilt was enhanced by his inability to forget, his prodigious memory which enabled him to repeat verses he had read only once years previously,

relentlessly reminded him of the shortcoming of a lifetime, and denied him the merciful amnesty for past offences which time brings to most of us. Throughout his life he felt guilty of what he had done in his childhood and youth".

Another interesting personality Sir Russell Brain describes was Chistopher Smart who in the possession of his mental faculties was just a mediocre poet. However, madness endowed him with a gift, and the most enchanted verses were written when chained to his illness. As Cinderella, a return to normalcy signified for him the lost of that fantastic realm in which he poured melodies into the most fitting words.

Dickens is included in these clever studies of genius. In Dickens he admires the capacity and talent to describe in an accurate way true clinical pictures of Neurological and Psychiatric Syndromes.

In all of his character portrayals the hand of the artist mixed with the scrutinizing eyes of a scientist presenting those wrecked lives with warm understanding and true love toward mankind.

After giving to everyone of Dickens' masterful description of physical and mental impairments his medical definition, Sir Russell concludes "But I have said enough to show that at a time when medicine itself was just only begining to recognize the importance of physical signs, the characters in the world of Dickens' imagination are so real that they have recognizable diseases of body and mind described with the accuracy and insight of a great clinical observer".

He doesn't limit his acute perception of art to those revealed through letters. It is a rewarding experience to see through his eyes, Grock, the inimitable clown, dissected in his comic feats.

The description of his performance and the unvelling of the hidden secret of our joy in response to his acting and its symbolism will remain a little gem in this interesting book.

In "Sitting for Epstein", the plastic art is the field in which many interesting dialogues give us the pleasure of witnessing the sculptor and Sir Russell engaged in the most intriguing give and take on a wide range of subjects.

Poetry and oratory, the power of words as a tool of expression, are another of the favourites of Sir Russell Brain's inquiries. It is interesting for men of letters and neurologists as well to follow his scintillating thought which links sound and poetry, intention and construction. The power of Dylan Thomas' poetry to evoque without being specific, is based on the reader having a storehouse of past experiences to detect the subtle meanings. Methaphors and the comic impact of a pun are also studied and it is interesting to regard the latter as "mental Diplopia" or a kind of mental double vision.

This is how Sir Russell Brain explains the abilities of genius to use words. "Nerve cells are grouped into functional patterns, which are best called schemas. Where the genius excells the ordinary person is that in some respect he is richer in schemas. This may mean that he has more nerve cells. We do not know, but it is quite possible for the same number of cells to be arranged either in simple or in complex patterns, just as a child's reader and Shakespeare's works are composed of the same twenty six letters, and the normal number of nerve cells is so large that differences of organization by themselves could account for profound differences of functional capacity".

There was a time in the History of Mankind when enlightened men dweling on Philosophy turned their minds to Medicine so as to round out their knowledge of human nature. That was the time in which Me-

dicine rose from the artesan level to that of an art, those where the socalled physician philosophers and among them were Phitagoras, Alcmaeon and Empedocles. Nowadays the two springs of human knowledge mix once again their findings in the quest for truth. Medicine and Philosophy are masterly managed in the books by Sir Russell Brain, "The Nature of Experience" and "Mind Perception and Science".

"The nature of experience"

Some of the sentences of these small but substantial books will give the reader a hint about the peaks of mental speculation to which the author climbs with his thinking.

"Philosophies illustrate the fairy story of the Emperor's clothes in reverse. The philosophy claims to be naked —the naked truth— but the eye of a child sees him to be wearing the oddest collection of old clothes, some inherited from the past, and some painstakingly made by the philosopher, like a caddisworm, from such materials as he happened to have at hand. Indeed, we may come to the conclusion that the important thing about truth is not that it should be naked, but what clothes suit it best, and whether it should not sometimes dress up for special occasions".

Human experience is disclosed in its various aspects and the philosophical point of view is checked against scientific knowledge of the brain.

Speaking about time-element in perception, Sir Russell Brain states "Since all transmission of physical energy takes time, and perception, depends upon physical energy transmitting light waves and sound waves to the body and nervous impulses within it, and since we do not perceive any object until the relevant nervous impulses reach the brain, our perception must always be later than the state of the object which it represents, only a fraction of a second later when the object is a piece of wool touching the skin, eight minutes later when the object is the sun, and many thausands of year later when the object is a star".

For the philosopher and the medical doctor this blend of the two sciences which provide man two powerful hands to wrestle with reality, is particularly fascinating.

All through the book, points of interest are treated with a keen sense of exactness. Vision and fantasy, were very well revealed from the hidden mysteries of the brain, in health and illness. The alteration in perception produced by drugs as Mescaline and LSD, shows the human machine distorting the sense data gathered from the physical world.

The awe aroused in everyone by a work of art is analyzed as well as the perceptual power of the artist to pour his feeling into sound, form or word and thus evoke in others the same sentiment.

Thus medicine, art, poetry and philosophy are finely interwoven into the fabric of a book captivating the reader.

"Mind perception and Science"

The same thing can be said about "Mind Perception and Science" in which with a neurological approach, speech and thought are studied. From the many interesting things written I extract this sentence: "Think of patterns. An atom is a pattern of electrons, a molecule is a pattern of atoms. There are patterns of patterns of patterns and so indefinitely. The most conplicated we know are in the brain. Not only are there twelve thousand million nerve cells out of which the pattern can be made, but nervous patterns exist in time, like a melody, as well as in space. If you look at a tapestry through a magnifying glass you will see the individual threads but not the pattern. If you stand away from it you will see the pattern but not the threads. My guess is that it is the nervous system we

are looking at in the threads while with the mind we perceive the patterns, and that one day we may discover how the patterns are made out of the threads".

The cerebral basis of consciousness, the marvellous working of the nervous system, and the human dwelling with "two worlds", the perceptual and the physical "world", are scrutinized, always giving his personal point of view to end with symbols and patterns which enable man to master the physical world and the complexity that this fact embraces.

For those who after following the current of his thought felt somewhat puzzled by some of the facts studied, Sir Russell mantains a very interesting and clarifying conversation with the reader and in the dialogues, crucial points of the neuro-physiology are discussed.

"Tea with Walter de la Mare"

Oh, that joyous place in the third dimension of the mind! Out of the common place that day by day sticks us to earth, need, survival and duty.

On the wings of poetry soaring high, on the peak of philosophy peering afar!

Thus over a cup of aromatic tea with Walter de la Mare, this thoughtful physician frees himself from the pressing duties of Medicine. But as a jealous lover Medicine never leaves him alone wherever he goes, she goes trying always to attract his attention to her.

And the mysteries of rhythm, music, and poetry fall as from force of gravity into neurology and beautifies it.

While the Latin people pour out their ideas over a little cup of coffee after lunch or dinner, or some other time of the day when they have time and feel like having a friendly talk, about ideals, politics, business or community gossip, the saxon descendants (and also the asiatic ones) are tea lovers, who mingle their favorite beverage's aromatic fumes with the most interesting and subtle topics of conversation. Scientists and doctors are not free from these interesting intervals in their routine and this has lead Ramon y Cajal to publish his "Charlas de Café" ("Coffee talk") and Sir Russell Brain, "Tea with Walter de la Mare".

It is a very interesting fact that physicians more than any other professional men need an interchange of ideas with people of different disciplines of thought, as medicine tends to unilateralize the trends of ideas.

Everyone is the owner of a little piece of the jigsaw of the landscape of life and that is what makes interesting and puzzling the mere fact of living and trying to understand why. Thus when people meet and discuss they are trying to match their slice of knowledge with that of another in a meaningful may.

The poet and the doctor. The rigidity of science and the fluidity of the intuitive poetry, profiting from each other's excellence.

How did Sir Russell Brain and Walter de la Mare come in contact?

Reading Walter de la Mare's book on "Rupert Brooke and the Intellectual Imagination" Sir Russell Brain came across the sentence "the little nowhere of the Brain" which aroused in him an interest to know more about the philosophical meaning of these few words with such a high intellectual content.

Thus Russell Brain states. "There is a sense in which all we experience lies within the brain. And yet we see our own bodies, of which the brain is part, through the activity of the brain itself.

So the brain seems to be dissolved into one of its own creations, to become "nowhere" in which nevertheless the whole of experience is

somehow located, a "little nowhere" in one of those phrases in which the logic of poetry defies and so enlarges the sense of the logician".

This led Russell Brain to write to Walter de la Mare about it. After an exchanged of letters an invitation to get together came and a friendship developed between them. Their interesting conversations are recorded in the book "Tea with Walter de la Mare".

Thus in the dwellings of the brain and its nowhere, seeking the hidden treasure of knowledge the poet and the scientist engaged in the most interesting enterprise.

From the ancient book of books the voice of Job emerges with the same anguishing question "But where shall wisdom be found? and where is the place of understanding?".

Through their several tea gatherings the most interesting problems were faced with the dreaming spirit of the poet and the exacting perception of a doctor.

As Sir Russell said in the beginning of the book they were talks about poets and poetry, time, memory, childhood, dreams, apparitions, horror, death and the unknown future, the unseen and the mystery of life. Let us hear just a part of their conversation.

"I mentioned —refers Sir Russell Brain— Jacquetta Hawkes's book. A Land, as a blend of poetry and science, which W. J. (Walter de la Mare) thought very difficult. «Why», he said, «must science need verification by observation? How much of one's experiences is unverifiable. Take the Society for Psychical Research: What self —respecting ghost would so— operate in their tests?» This led us to talk about ghost stories and he recommended those of Le Fanu and Henry James. We talked of the influence of the body on the mind, and conversely, which led to a discussion of the postures adopted by Buddha and by Yogis. He thought there was something to be said for assuming a special posture when meditating".

Sometimes it is difficult to find the right companion one to provide the needed contrast to ones own experience. An ideal combination? The doctor and the poet. Thus, all through the book the most interesting topics were illuminated in those visits to Walter de la Mare at his home. To comprehend life in all its variety it is important to be capable of being in tune with another's trends of thought. That is a lesson thot can be learned from the wide circle of acquaintances Sir Russell Brain has outside the medical profession.

Sometimes doctors don't realize what they are missing until they run across poetic expression. And to those who exclaim what is the use of a poet. Let us have T. S. Eliot the British poet answer them: "Poets he said, can be useful in three ways: they can preserve the beauty and integrity of language; they can be entertaining; and more important they can make us from time to time a little more aware".

To be "more aware", means to broaden life's scope, because it is not a long life that matters, but a fuller, richer, and more intense one.

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TRATAMIENTO DE LA EPILEPSIA CON METAMINODIAZEPOXIDO

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En 1959 los autores pudieron observar que en algunos enfermos epilépticos, que no mejoraban con hidantoinatos y fenobarbital, se obtenía cierta mejoria con el Librium. Estas observaciones, y las anteriores de Kaim y Rosenstein, les indujeron a estudiar desde el punto de vista experimental y clínico las propiedades anticonvulsionantes del Librium.

Comprobaron en el gato que el Librium tiene una potente acción protectora frente a las convulsiones provocadas por el metrazol, originando una desincronización prolongada del electroencefalograma que impide el ataque convulsivo. Al parecer este efecto se produce por acción del Librium sobre las estructuras del mesodiencéfalo que integra el sistema reticular activador ascendente.

A diferencia de los barbitúricos, el Librium no produjo depresión de los potenciales corticales evocados, ni tampoco se observó ninguna disminución de la conducción de los estímulos sensoriales a la corteza.

A la vez que estos estudios farmacológicos, los autores estudiaron el efecto del Librium en un grupo de 15 enfermos epilépticos, 13 de ellos graves y con transtornos psíquicos marcados.

En general se comenzó con una dosis de 75 mg diarios, aumentando después en forma progresiva hasta llegar a los 150 mg y al día. En algunos enfermos se sustituyó la medicación antiepiléptica (hidantoinatos, luminal) por el Librium de manera paulatina. El tiempo de observación fue variable, 4 ½ meses en la mayoría de los casos.

De los resultados obtenidos, experimentales y clínicos, deducen los autores que el Librium tiene propiedades anticonvulsionantes superiores al difenil-hidantoinato sódico y a los barbitúricos. Su acción sobre los trastornos psíquicos que acompañan a los ataques (confusión, estados crepusculares, distimias) es la más potente y eficaz que hasta ahora han observado. En todos los casos se obtuvieron resultados favorables y, en muchos de ellos, sorprendentes como en estos dos casos:

M. P. V. — Enferma de 31 años que ingresó en el hospital el 5 de noviembre de 1955. Ataques convulsivos desde los 14 años con frecuencia dos o tres veces en el día. Estados de gran mal y fases de excitación en forma periódica. El 17 de octubre de 1960 se inicia tratamiento con Librium a razón de 75 mg diarios al comienzo y, después, 150 mg. Durante el período de observación, 4 meses y medio, se comprobó una considerable disminución de las crisis presentándose sólo en número de 2 a 6 al mes. El 2 de febrero tuvo 6 crisis convulsivas consecutivas y se administró fenobarbital, por vía parenteral, sin interrumpir el Librium. No se han presentado fases de excitación y durante este período no ha sido necesario su traslado al departamento de enfermos agitados.

MO. D. V. — Enferma de 35 años. Ingresa el 6 de setiembre de 1952. Ataques convulsivos desde los 18 años, con frecuencia 3 ó 4 por semana, con estado confusional después de las crisis. Reacciones de Iues positivas que fueron negativas con el tratamiento específico. Los tratamientos con los antiepilépticos habituales no han sido satisfactorios. El 17 de octubre de 1960 se inicia tratamiento con Librium, al principio 75 mg diarios y más tarde 150 mg diarios. Tiempo de observación, 4 meses y medio. A los 5 días de comenzar el tratamiento se muestra rebelde, moderadamente agitada y rehusa el medicamente. Se consigue que continúe tomándolo y no ha vuelto a tener ninguna crisis convulsiva. Las fases distímicas han desaparecido también y no ha hecho falta internarla en el pabellón de enfermos agitados.

Los autores destacan que con el Librium los enfermos no tienen entorpecimiento de sus funciones psíquicas ni motoras. Al contrario, en los 13 casos, que además de los ataques tenían marcadas alteraciones mentales, éstas mejoraron de manera notable.

Los exámenes de laboratorio no revelaron ningún efecto tóxico especial, sin que se observasen alteraciones del cuadro hemático ni de la funcionalidad renal o hepatica.